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PULMONARY MYCOSES

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Topical Outline

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List of Illustrations

PULMONARY MYCOSES

Purpose : A case of pulmonary moniliasis which came to autopsy at the Massachusetts Memorial Hospitals last year stimulated the interest of the Bacteriology Department in the subject of fungal infections of the lung. Accordingly , a systematic review of the literature was made in an effort to discover the incidence of the pulmonary mycoses. Following this , a study was made of the sputa of 31 patients in a tuberculosis sanatorium in an endeavor to find the percentage of double infections.

Three cases which were called to the author's attention during the period of this study are herein reported for the first time.

Limitation of Field : Because of the vast amount of literature available on this subject and the multiplicity of etiologic agents concerned , it was deemed advisable to limit this discussion to three groups of fungi. Monilia and Aspergillus were chosen because they are most commonly found in the sputum. Coccidioidal infection has attained such prominence during the past several years that it seems probable it will be very important in the future. Actinomyces is not included because the current concensus is that it is a bacterial, not a fungal , agent.

General Remarks

Medical Mycology : The term mycosis is used to describe an infection the etiologic agent of which is a fungus. Because of the wide distribution of fungi in nature and as saph-

rophytes on man, their presence in lesions or exudates is not conclusive proof of their relationship to that pathological process.

Fungi are members of the plant kingdom and are Thallophytes having undifferentiated roots, stems and leaves. The group is an indefinite one, including many different types of lower plants. Fungi are especially characterized by the absence of chlorphyll which prevents their using the energy in sunlight, and they must resort to chemical energy produced by decomposition.

Many of the fungi are thread forms , although this is not a constant characteristic. Each thread in the mycelium is known as a hypha, which may be septate or coenocytic. Reproduction takes place usually by means of spores.

Classification :Pleomorphism within the group makes classification difficult. The basis is usually the type of spores, manner of formation , and the appearance of the mycelium. The colonial appearance is only of diagnostic value when the media is constant. Biochemical reactions are of importance in the identification of yeasts and Moniliae. Serological methods such as alexin-fixation, agglutinative , and precipitative reactions are becoming increasingly useful in the determination of species of Moniliae which possess a type specific polysaccharide. In addition to the botanical classification , numerous clinicians have devised their own systems. Typical are those by Bakst (I), and Castellani (II).

I. 1. Filamentous forms - Actinomyces , Vibrio , Anaeromyces ,

Cladothrix, Leptothrix.

2. Yeast-like organisms peproducing by thallospores - Blastomyces, Torula, Monilia, Oidium, Oospora.

Reproducing by ascospores - Saccharomyces, Willia, Endomyces, and Coccidioides.

3. More complex forms - Aspergillus , Penicillium, Acremoniella, Mucor, Rhizopus-mucor, Sporotrichum, Acladium.

II. 1. Due to yeast-like fungi : Blastomyces, Crytococcus, Saccharomyces, Monilia, Endomyces.

2. Due to filamentous fungi :

a. Of the slender type : Nocardia, Anaeromyces, Vibriothrix.

b. Of the larger size : Oidium , Hemispora.

c. With characteristic fruiting structures and conidia : Aspergillus, Penicillium, Mucor, Rhizopus-mucor, Acremoniella, Sporotrichum , and Acladium.

Pathogenicity of Fungal Infections : Fungal infections are usually milder than bacterial infections since they tend to run a more chronic course. However, they may be very per - sistent and progressive, eventually endangering life by metas- tases to internal organs. Due to their low invasive power , most infections occur in debilitated individuals, or in those whose occupations predispose or expose them to massive or re- peated infection. Although the mechanism of fungal pathogenesis

is not definitely known, pathogenic fungi are believed to injure by their mechanical action. The acute lesions produced by highly virulent strains suggests a mechanism similar to that in bacterial infections - e.g. toxins. As yet, there are in the literature no entirely convincing reports of the presence of toxins.

Symptoms : There are certain symptoms in common to all the bronchomycoses whatever the etiologic factor. In mild cases, there is slight bronchitis with mucopurulent expectoration in which the fungus is found. In severe cases , the patient presents the signs and symptoms of tuberculosis with severe fever and haemmorhagic expectoration. Most bronchomycoses , unless too far advanced, benefit by treatment with potassium iodide.

The prognosis varies a good deal according to the causative fungus and the degree of involvement. In general, mild cases are amenable to treatment , while the far advanced are hopeless.

Pathology : The lesions produced are of several types. As saphrophytes , the fungi grow merely on the body surface , or invade the upper layers of the epithelium. As parasites , they may give rise to tissue changes, abscesses and granulomata. The characteristic lesion is a necrosis of the tissues with softening , an accumulation of leuokocytes and the formation of pus. The abscesses are surrounded by a dense layer of fibrous tissue infiltrated with mononuclear and sometimes giant cells.

Fungi in Sputum : Though many authors are of the opinion that primary fungal infections of the lung are more common

than is usually thought, the presence of yeast-like or other organisms is not in itself sufficient evidence on which to base a diagnosis of primary pulmonary mycosis. However, such a finding , in the absence of any other definite etiologic agent , gives strong support to such a belief. By careful clinical and laboratory studies , fungi can sometimes be established as the primary etiologic agent in certain cases of pulmonary inflammatory processes.

Fungi may be present in the respiratory passages as saphrophytes. As secondary invaders , they may complicate disease when associated with tuberculosis , bronchitis , bronchiectasis, abscess and carcinoma. Less frequently , they may be the primary cause of the disease and produce varied lesions. Among the fungi reported to have been isolated from the sputum and proved as definite primary infections are : Penicillium, Aspergillus, Coccidioides, Monilia, Torula, Blastomyces , Sporotrichum, and Cryptococcus.Mold spores are so ubiquitous that Koch's postulates should be borne in mind.

The fungal flora of the normal individual should be established before too much significance is attached to the finding of some of these organisms in sputum.

Differentiation of pulmonary mycoses from tuberculosis : Bakst and other authors have summarized points which should be kept in mind when a definite diagnosis is difficult to make . The patient should always be studied as a whole. The presence of an atypically located pulmonary lesion together with a discharging sinus in the chest or neck, and the concommitant pres -

ence of a dermal or joint lesion is very suspicious. The demonstration of a fungus in both the sputum and pus is helpful in a case of this sort.

Other diagnostic aids include the fact that diseases produced by fungi usually proceed slowly with the production of a good deal of fibrosis. The constitutional symptoms characteristic of tuberculosis may not be as marked in mycoses. X-rays rarely but sometimes suggest pneumomycosis. Pulmonary disease involving only the lower part of the lung is rarely tuberculosis as this disease usually involves the ubber lobes. Pneumomycosis may also simulate neoplasms.

One should remember that the pulmonary mycoses are considered clinical entities. A diagnosis should be made only when the laboratory findings have been confirmed and a pathogenic species of fungus has been repeatedly isolated from sputum collected with all due precautions. Since fungi produce lesions very similar to those of tuberculosis , all cases of clinically diagnosed tuberculosis which are not supported by laboratory findings should have the sputum examined for fungus. Several authors believe that a routine culture for fungus should supplement every examination for tubercle bacilli.

ASPERGILLOSIS

Aspergillosis is an inflammatory disease caused by one or more species of the genus Aspergillus , an organism which seems to have a marked predilection for the tissues of the respiratory system. The disease usually runs a chronic course and

resembles the infectious granulomata.

Historical Note

The literature on the Aspergilli dates back to 1729 when Michali published a description of the first member of this group broad enough to be applicable to any microscopic fungus with a stalk and spore bearing head. In the ensuing 200 years , some 300 species have been isolated and named by investigators.

The first observation of Aspergilli in human tissues was made by Bennett[1](1842) who described this fungus as a rather harmless and widely distributed parasite which at times caused pulmonary infection in man and animals. The first scientific description of the fungus with an accurate determination of species was made by Virchow in 1856.

True infection of the lung occurs rarely in man. The majority of cases reported have been from France , and the disease is known in Germany. Aspergillosis may be primary , or secon - dary to some such condition as tuberculosis, pulmonary gan - grene , carcinoma , and bronchiectasis.

A considerable number of cases of primary pulmonary aspergillosis was reported in France some years ago, notably by Renon.[2] The disease was apparently occupational since it occured in individuals engaged in industries which peculiarly subjected them to the possible inhalation of large numbers of spores. These occupations included the "gaveurs des pigeons" who fattened squabs for the marked by filling their mouths with finely chewed grain , and then forcing it with their tongues

into the oesophagus of the bird, and the "peigneurs des cheveux" who prepared hair for the manufacture of wigs by mixing it with cornmeal to remove oil , and then combing it out. In both cases the source of the infection is obvious, although in the former the infection may have come from the bird, since some of the pigeons were found to have aspergillar infections of the mouth. On the North American continent only isolated cases have been reported , dealing with the pulmonary or bronchopulmonary in - volvement , often with asthma.

Mycology

Habitat : Aspergilli are widely distributed in nature , and along with Mucor and Penicillium constitute the common contaminants encountered in bacteriologic work. The organisms are abundant on dead and dying plant tissue , in ripe fruit , or in stored bulbs or barks of trees and in secretions and exudates. A large number of species comprise this group. Thom and Church[3] have 350 strains in their present laboratory collection. With few exceptions, the members of this group are pure saphrophytes, non-pathogenic for man or animal. The true parasitic members of this group seem few in number,although more than 60 different species have been decribed at various times as occuring in connection with various kinds of human or animal diseases. Some of these species have been found as harmless organisms in the respiratory tract,or as secondary invaders in various types of bronchopulmonary disorders.

The parasitic members of the Aspergilli are pathogenic for

most susceptible bird, while rabbits and guinea pigs are the most convenient laboratory animals.

A. fumigatus and its variants (A. nigrescens Robin, A. malignus Lindt) A. Lageni Hallier, and A. nolting) are commonly considered the most pathogenic, although A. Niger, A. repens, A. flavis, A. herbariorium, and A. versicolor have been mentioned.

When to this multitude of supposedly pathogenic Aspergilli are added the vast number that have at various times and by different investigators been recovered from disease processes, the number becomes an imposing army difficult of management and classification. Thom and Church[3] correctly point out the difficulty in a proper evaluation of case reports, when one recalls that many of these investigators have often had only a limited knowledge of molds and of the cultural methods employed in their isolation. (Since such animal experiments as were employed commonly gave negative results, it would seem that most writers have shown an appalling disregard for Koch's postulates). The relationship of most of these organisms to the underlying pathologic lesions from which they were isolated remains to be proven, the only exception being A. fumigatus.

Morphology; Aspergilli are mycelial fungi; their bodies consist of branching filaments composed of cells placed end to end, growing mostly at their tips and extending into the substratum. Some ramify deeply throughout great masses of material; others which are more closely dependent upon immediate access to the free oxygen of the air grow widely over the surface and

penetrate only the few outer millimeters of the unbroken surface.

The genus Aspergillus is recognized by the characteristic arrangement of conidiophores and conidia. An enlarged cell of the vegetative mycelium, known as the foot cell, throws up, under favorable conditions of moisture and heat, erect stalks or conidiophores which terminate in a swollen portion, the vesicle. From these vesicles but out a large number of spore producing cells - sterigmata which have a characteristic tenpin form, in some species simple and unbranched, in other branching to produce secondary sterigmata or verticils. From the tips of these sterigmata are repeatedly cut off conidia (spores) which are at first cylindrical segments cut from the tip of a narrow tube. Each is quickly succeeded by a newer cell cut from the same tube. Thus there is formed a chain of spores which lengthens actively at the point of origin. Each spore or conidia, growing quickly swells and assumes the size, shape and markings characteristic of its species. The whole mass at the tip of the stalk thus forms a head which may vary from globose if its elements are radially directed from the central vesicle to columnar if only a cluster of sterigmata are borne upon the very tip and the chains adhere to form a solid mass. The form assumed is more or less characteristic and definite for each race.

Some spore heads produce enormous numbers of spores or conidia, varying according to the species from two to ten micra in diameter. They are so light that they float readily. Some are waterproofed so that they will float upon the surface of

water a considerable distance before they sink, absorb water and grow. Others are variously sticky, roughened, eroded or chiseled to favor adherence to moving objects. These characteristics favor a wide diffusion of spores. In some species of Aspergilli, ascospores are formed, so they are "perfect" fungi, classified with the Ascomycetes. Of the common species, ascospores are formed most readily by A. glaucus and A. nidulans. The perithecia develop from coiled hypae and, when mature, they appear on the surface of the colony (i. e. A. glaucus) as small yellow dots easily visible to the naked eye. In some cultures they may be developed in large numbers. The wall of the perithecium which is very firm, is composed of polygonal cells. The ascospores, eight in number, are contained in clear oval asci, surrounded by much loose, cellular tissue. In some cases the asci are few in number. Not infrequently are found what appear to be perithecia but which contain no asci. These are sclerotia. In some species only such sterile sclerotia have been found, no asci being known. In still others, neither perithecia nor sclerotia have been demonstrated.

Cultural characteristics; With the development of improved methods of isolation, Aspergilli have been found to grow readily on a wide range of laboratory media, either acid or alkaline. It has therefore been possible to obtain pure cultures and study their reactions to selected media. Solutions and media made from the formulae proposed by Raulin, Cohn and Czapek have been used as a basis to test the availability of particular nutrients to individual species. In their metabolism, they

have been found to utilize inorganic salts of all the usual elements except carbon with iron and manganese favoring their growth and multiplication.

Aspergilli grow well at temperatures ranging from 20 to 37 degrees C. the latter being optimal, so that they grow well in the tropics. They can apparently tolerate very high osmotic pressures and get along with little water.

When infected material harboring Aspergilli is inoculated and incubated, there appears in from 24 to 72 hours on solid media, white round or oval plaques which rapidly increase in size, showing a tendency to coalesce and adhere to the medium.

The color and character of the growth depends upon the species. A. fumigatus develops a rounded colony, green in the center, surrounded by a white periphery. After three days, the white halo disappears forming an entirely green colony. The surface is irregular with a dry, filamentous periphery and a powdery center which is slightly adherent. Conidiophores are formed in from three to four days. In ten to twelve days the colony becomes smokey and finally is a dense, velvety mass. A. niger group gradually becomes covered with an inky black, granular powder. Depending upon the species, type of culture medium and temperature conditions, the culture may remain smooth, become wrinkled and convoluted, or form concentric rings.

Identification of Species.

Two tendencies have been encountered in the discussions of identification;- 1, the description of new species for every

change in size of head or length of stalk, or shade of color, and on the other hand, 2, lumping all forms with even a superficial resemblance into such complex heterogeneous aggregates that the names used ultimately came to be meaningless.

The problem of identifying species is so complicated by the changes induced by environment upon the structure and appearance of the mold colony. As they appear in nature, moldy masses usually contain more than one species, and the individual species may be so far influenced by its associates as to render it scarcely recognizable by gross or microscopical examination. Before these effects were understood, the students of fungi described a great many species, giving the color and measurements found in particular collections upon more or less vaguely described substrates.

Differentiation of species depends to a great extent upon the color of the spores which is fairly constant if the culture is examined at the right stage of growth. If too young, the spores have not developed sufficiently and the color of the surface of the colony is white. If examined too late, the color becomes darker and less definite.

Frequently the vegetative mycelium develops a different color, best observed from the bottom of the culture dish, usually red or yellow. This color is not so constant or characteristic as that of the spores, and is more dependent upon the composition of the medium.

A number of species are so nearly alike in color that the final identification must always be based upon microscopical examination of the spore heads. The characters to be observed are

the size and form of the vesicle, the number and arrangement of the sterigmata, the presence or absence of secondary sterigmata, and the size and form of the conidia. All of these characteristics taken together give the spore head itself a characteristic arrangement. The spores tend to be arranged in a dense mass which may be globular, oval or cylindrical in form. The height of the conidiophores is also used as a point in classification. Where present, the position and color of the perithecia and the form of the ascospores are important, but they are produced rather infrequently by most varieties. In this generic group, there is a large number of species, races and strains. Thom and Church[3] split this whole number into 16 species aggregates which are fairly easily separated when pure cultures are studied with a compound microscope. Within these species aggregates, the task of separation is more difficult, but they name 66 species already described and probably identifiable upon morphological bases. However, a large number of these species ~~are~~ is rare and not important.

Animal Experimentation

There is a common belief that *Aspergilli* are purely saphrophytic, that they can live only in pre-existing lesions, and that they cannot attack living tissues because they have no primary pathogenic powers. To prove the fallacy of this hypothesis, numerous experiments have been performed.

Saxer[4] found that *A. fumigatus*, experimentally inoculated into laboratory animals, produced lesions which varied according to the virulence of the strain and the dose. Many strains iso-

lated from the air or vegetable matter were non-pathogenic, while strains recently isolated from spontanteous infections might exhibit a surprising degree of virulence, a small dose of spores suspended in saline and inoculated intravenously killing a pigeon overnight. In such acute infections, no lesions were apparent. With smaller doses or less virulent strains, multiple miliary abscesses were produced especially in the lungs. Intravenous inoculations in rabbits usually caused death within three to five days, and the most striking lesions were multiple miliary abscesses in the cortex of the kidney. Subcutaneous or intra-abdominal inoculations produced localized lesions usually not fatal. Lapham[5] summarized the results of nine rabbits inoculated intravenously with varying doses of spores from a pure culture of A. fumigatus. Of three rabbits inoculated at St. Augustine, Florida, one died in twenty, one in twenty-four and one in forty hours. In all, the lungs were solid as in lobar pneumonia; the spleen, liver and kidneys were greatly congested and the mycelium was found in these tissues from which the organizm was isolated in pure culture. Three rabbits were inoculated at the Johns Hopkins pathological laboratory. In one dying at five days, gross lesions of the lung were not conspicuous, but the liver and kidney had the appearance of miliary tuberculosis. The second rabbit was killed after two weeks and showed a typical miliary tuberculosis of the lung, liver, spleen and kidneys. The third rabbit remained well. Three rabbits inoculated at the Hygienic Laboratory, Washington, D. C. were killed after twelve days. The lungs of the first were typically tuberculous in appearance

while those of the second and third were solid as in lobar pneumonia .Microscopically , tubercles were seen in all the livers, spleens, kidneys and lungs.

Martins[6] inoculated a rabbit intravenously and death occurred in 48 hours , with a general visceral congestion ,serosanguineous exudate from thenpleural and peritoneal cavities, pleural pulmonary adhesions , and atelectasis. The organism was recovered in pure culture from the viscera. The same culture injected intraäbdominally was nonpathogenic for a guinea pig. Nicaud[7] conducted a series of experiments with A. fumigatus ,isolated from sputum, using both guinea pigs and rabbits. Subcutaneous inoculations produced large or small localized nodules,the center of which consisted of many spores and mycelial fragments surrounded by polymorphonuclear and,rarely, mononuclear cells.A small nodule might consist of a single filament encircled by polymorphonuclears. Intraäbdominal injections gave rise to a localized or generalized peritonitis frequently with great extension. The local reaction often developed an enormous inflammatory mass causing a fatal intestinal obstruction. Histologically,the lesions were similar to the subcutaneous nodules without mucous irritation. Intrapulmonary and intrapleural injections produced nodular lesions. The reaction to intravenous inoculation depended upon the dose, massive doses producing a fatal septicemia in ten to fifteen days. Smaller , repeated injections took longer to produce the characteristic lesions with several months of weakness and paralysis. The pulmonary lesions were those of a chronic congestion , while those of the kidneys showed sclerosis and

necrosis.

Nicaud[6] concluded that the nature of the experimental lesions makes disputable the term "Aspergillus pseudotuberculosis". No matter how closely lesions resembled those of tuberculosis, careful analysis proved them entirely different from a typical nodule. Experimental lesions were entirely different from those in human aspergillosis.

Henrici[8] produced a rapidly fatal haemmorhagic pneumonia is pigeons by causing spores to be inhaled. Only very acute infections resulted from this method. On the other hand , by feeding wheat overgrown with Aspergillus , he succeeded in 50% of pigeons in obtaining an infection of the air sacs, fatal in six weeks, very similar to the natural disease. Microscopically,the experimental lesions were characterized by extensive necrosis with some suppuration in the vicinity of the organisms. Some fibrosis was produced in the lung nodules. In the lesions where the fungus reached a surface exposed to the air , there were branched segments of mycelia with conidiophores at various stages of development. In the miliary abscesses produced by intravenous inoculation, there were small abscesses composed of radiating filaments.

Renon[2] pointed out the difference in the experimental lesions produced by A. niger and A. fumigatus. A. niger produced very slight lesions in no way comparable to the large confluent caseous pseudotubercles,produced by A. fumigatus. This he belived due to the more rapid phagocytosis of A. niger and not to the difference in their respective optimal temperature for growth.

Bethune and Moffatt[9] conducted an experimental study of the effects of A, niger on rats, guinea pigs and rabbits.They found that inhalation of A. niger, a common component of dust and food, produced chronic pulmonary granulomatous lesions,regressive in nature. There was no caseation or abscess formation, and the fungus did not produce mycelia or invade tissues. The superimposition of this fungus on a regressing tuberculous lesion was non-exciting in character. Inhaled spores were rapidly engulfed by alveolar phagocytes and became destroyed within these cells up to fifty days. By this time the phagocytes fragmented them and no cultures from the lungs were obtained after this time. No positive cultures were obtained from the trachea and bronchi after inhalation since spores were rapidly fixed by phagocytes. No evidence was found to favor the theory that A. niger produces extensive fibrosis and nodular calcification seen in some X-ray plates. To produce such fibrosis and calcification, the initial lesion if caused by the fungus must have been extremely widespread and of a seriously debilitating nature and produced by the inhalation of very large amounts of spores. If such were the case, the disease in both acute and chronic forms should be very much more common , especially in grain workers.

Serology

Some authors believe that A. fumigatus elaborates a thermostable toxin which, when injected into suitable laboratory animals, causes severe prostration, tetanic and paralytic convulsions, and in sufficient doses, death within a few hours. Cecci and

Besta (cited by Lapenta[13]) found this destroyed at 120°C. Martin[14](1929), contrary to others, found no exotoxin, but the possible existence of an endocellular toxin which acts on nervous tissue.

Attempts to demonstrate agglutinins,precipitins, and complement - fixing bodies in animals' and patients' sera by various investigators have thus far led to inconclusive results.

M. Legroux[15] was able to elicit a specific allergic cutaneous reaction as well as a focal reaction in the lesions by means of an aspergillar antigen in primary and secondary aspergillosis. Schiff[16], Craven,[17]and Sayers and Meriweither[18]have confirmed the presence of a specific allergic reaction. Lapham[5] found that cases of primary aspergillosis gave a positive tuberculin reaction , while Nicaud[19]observed that patients with advanced tuberculosis reacted to aspergillar antigen. Macaigne and Nicaud[20]found that cases with old fibro-caseous tuberculosis gave a more marked reaction to aspergillar vaccine than did patients with pure aspergillosis.

Symptoms

A. fumigatus is the most important etiologic agent in the production of this condition, the portal of entry being the upper respiratory tract or the oral cavity. The clinical manifestations vary greatly ; most often they simulate those of tuberculosis or bronchopneumonia. Schneider summarized the symptoms as : insidious onset , anorexia, night sweats , loss of weight, productive cough , purulent sputum(often blood tinged) and frequent hemoptyses. In general the signs and symptoms differ but

little from those noted in other types of bronchopulmonary lesions.

Jacobson [10] distinguished two types of pulmonary aspergillosis : the acute and chronic. In the chronic type the symptoms include asthenia, loss of weight , anorexia, night sweats,cough and a slight evening rise in temperature. Sooner or later ,the cough becomes productive , and the sputum is frequently blood tinged. Two important points in the recognition of this infection include frequent haemmorhages , and the fact that even patients who have been ill for a long time do not appear as ill and emaciated as those with a similar degree of tuberculous involvement.

In the acute type, the patients exhibit all the signs and symptoms of a severe pulmonary infection. They are prostrated to a degree far more severe than in the case of pneumonia , and the corresponding signs of toxemia are correspondingly severe. This is probably due to a thermostabile toxin produced by A. fumigatus.The physical signs and X-rays findings are similar in all essentials to those usually observed in similar types of disease except that there is apt to be more extensive cavitation. Lapham[5] , from her survey of the cases reported in the literature , concluded that there are two types : wet and dry. Of the wet or parenchymatous type, there are varieties corresponding to the location and the tissues involved. Where the bronchial mucosa are attacked , they may become almost black from congestion,ulcerations may be eroded ,and patches of membranes formed.Pathologicallyand clinically this is the bronchitic

type. Other cases were characterized by emphysema and pneumonia. In the dry or pleuritic type, the spores are carried to the periphery of the lung, are deposited there and attack the pleural surfaces. This causes congestion, thickening and sometimes bands of adhesions. In the pleuritic type of aspergillosis, pain is the first and often the only symptom. Mieres[11] reported the case of a woman with pleurisy at the right base who had such severe pain that hepatic colic was diagnosed and a cholycestectomy performedn. After two years in a tuberculosis sanatorium, the proper diagnosis was made and she had a prompt recovery after iodide therapy.

Hamman[12] pointed out that pneumomycoses may suggest, among other things, new growth; and a lesion of the hilum and lower lobes suggests fungi. Some cases reported as primary aspergillosis have really been secondary to some other disease, traces of which have been obliterated by the aspergillosis. On the other hand, it is quite probable that some cases of primary pulmonary aspergillosis are overlooked, being mistakingly diagnosed as tuberculosis.

PATHOLOGY

The infectious process, resulting from invasion of the tissues by Aspergilli, closely simulates that produced by the tubercle bacilli. There are two general types: the parenchymatous and the interstitial. In the parenchymatous form, the pathologic picture depends upon the area and the character of the tissues involved. When the infectious process is limited

to the mucous membranes of the bronchial tree,there is a deep and extensive congestion, with or without an associated membranous patchy involvement and mucosal ulceration. When the fungi become lodged in the alveoli , the resulting process may either remain confined to the pulmonary tissues , or the organisms may find their way into the smaller bronchi,eroding their way through , and riddling the lungs with variously sized tubercles and cavities. There have been reported cavities of fairly large size communicating with larger bronchi.

When the fungi are lodged at the periphery of the lung and attack its pleural surface, there results a congestion and inflammation and finally a thickening and fibrosis with or without bands of pleural adhesions resulting in pleuritic pain.

In the interstitial type of infection, the spores pass through the alveolar walls and find their way into the interstitialtissues . The resulting lesions closely resemble those described above, and do not differ materially from the process produced by the tubercle bacilli.

One feature common to all types of pulmonary aspergillosis is the frequent presence of atheromatous lesions throughout the arterial tree of the respiratory tract. In addition to invading the coats of the arterial walls, these organisms may also cause the formation of thrombi within the lumen of the involved vessels, continue to multiply and form colonies within the clots formed therein.

Microscopically, the lesions are granulomatous. The cellular infiltrate may be diffuse or circumscribed ;tubercle

formation often occurs. Surrounding the organisms are polymorphonuclear neutrophilic leukocytes, lymphocytes and giant cells, frequently encapsulated by a fibrous layer. Central necrosis may be present or absent.

COURSE AND PROGNOSIS.

Broadly speaking, the disease runs a chronic course and may last for years without seriously affecting the patient. In acute parenchymatous types or even in the chronic, when certain complications are superimposed, the disease is rapidly fatal and the prognosis is poor. However, prompt treatment may favorably affect the prognosis of the more serious forms.

Diagnosis

The diagnosis of pulmonary aspergillosis depends upon the constant presence of a pathogenic species of Aspergillus in uncontaminated single specimens of sputum, collected with the usual precautions for fungous work. The sputum may be examined directly in a fresh cover slip mount using 20% potassium hydroxide to clear the cellular elements. In stained smears the organisms are Gram negative.

Pure cultures are essential for the accurate differentiation of species. In all suspected or doubtful cases, recourse may be had to guinea pig or rabbit inoculations with infected material.

Primary pulmonary aspergillosis must be differentiated from chronic pulmonary tuberculosis, bronchopneumonia, neoplasms, bronchitis and pleurisy. When pulmonary aspergillosis is secon-

dary to other types of respiratory infections, the clinical diagnosis of the existing condition becomes a difficult matter unless supplemented by laboratory methods.

TREATMENT

The successful treatment of aspergillosis is dependent largely upon an early diagnosis and the available employment of therapeutic agents. As in all fungal diseases, wholesome food, good air, plenty of rest and a proper hygienic environment are of the utmost importance in the management of the disease.

The patient should be encouraged to give up an occupation which brings him in contact with birds or dust. If possible, a change of climatic or atmospheric environment is often beneficial. Treatment of any underlying constitutional debility is of extreme importance. Unfortunately, in most cases in which it plays a part, the debilitating condition is in itself of the hopeless type and the secondary aspergillosis merely plays the part of terminal infection.

Various remedies such as lipiodol instillation of the bronchial cavities and a number of drugs have been tried by different investigators with no definitely helpful results. Until some specific remedy is discovered, the sodium and potassium iodides seem to be the mainstay of treatment. These should be given in large doses and to the individual tolerance point. Iodine is most destructive to Aspergilli and seems to serve to cause an absorption of infiltration. Although iodides are generally contraindicated in tuberculosis, Lapenta[13] reported a case of combined aspergillosis and tuberculosis which improved under

treatment with iodides due to a general amelioration of health caused by enhanced immunity.

Dr. Wherry quoted by Schiff[16] suggested that it would be interesting to try the effects of chloroform anaesthesia on patients with pulmonary aspergillosis , since chloroform in high dilutions was most effective in destroying aspergillar spores.

Vaccines have apparently been beneficial in some cases of mild aspergillosis. A typical method is that used by Craven[17] who prepared a vaccine by washing a growth of slant with physiological salt solution , grinding with sand or glass beads,and heating it in a water bath for one hour at 56°C. Dilutions of 1:100 and 1:1000 were used for skin tests , and that to which the patient responded was made the basis for the early therapeutic doses. The initial dose of 0.1 cc. was increased as rapidly as tolerated at three - day intervals. The vaccine was continued as long as there was improvement , and no untoward effects were noted in patients treated one year. If reports in the literature are not to be questioned, much can be accomplished with our limited therapeutic resources when aspergillosis is diagnosed early and treated diligently.

References

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Bronchopulmonary Moniliasis

Introduction

Bronchopulmonary moniliasis may be defined as an infection of the respiratory organs in which a pathogenic species of Monilia appears to play an important etiologic rôle. The clinicopathologic condition is associated with the constant presence of Monilia in the pathologic lesions and secretions of the respiratory tract.

The relationship of Moniliae to human disease was first demonstrated in 1839 by Langenback who found the organisms microscopically in patches of thrush on the oral mucosa, pharynx and gastro-intestinal tract of a patient who had died of typhus. Charles Robin named the organism Oidium albicans in 1843. Castellani[1] pointed out the relationship of Moniliae to bronchopulmonary infections in patients in Ceylon.

Since then pulmonary moniliasis has been observed and studied in various parts of the world-especially the tropics - by a number of investigators. Case reports have come from Seattle to Siam, from Baltimore to Buenos Aires. The only continent in which the disease seems to be absent is Australia. The first case in this country was reported from Baltimore in 1915 by Boggs and Pincoff[2], and since that time the disease has been observed over the entire continent although relatively few reports have occured in our medical literature.

Bronchomoniliasis is much more common in tropical countries than in the temperate zone, but it occurs in all climates, and

probably with much greater frequency than is generally recognized. Realization of the cosmopolitan nature of Monilial infection, clinically indistinguishable as it is from tuberculosis, will lead to a growing appreciation of the value of prompt diagnosis of this condition, which in its mild form readily yields to treatment with iodides, but which when neglected or treated as pulmonary tuberculosis, usually ends fatally.

Moniliae are widely distributed in nature. They occur as saphrophytes on dead leaves, fruits and decomposed woods. They have also been found in human and animal excreta, as well as on the mucosa of the mouth, skin, upper respiratory and gastro-intestinal tracts of apparently healthy individuals. The current belief is that some members of the group which inhabit the human tissues as saphrophytes may under favorable conditions assume parasitic habits, become pathogenic, and give rise to disease.

Mycology

Mode of Infection. The mode of infection of this disease is a matter of conjecture. Undoubtedly the fungus exists saphrophytically in the mouth and becomes pathogenic under favorable conditions. Farah[3] and Jacono[4] state that it may be transferred from man to man. Grossi and Balog[5] believe that the most frequent carriers of the organism are dried fruit and straw. Mautner[6] calls attention to the frequency of the disease among those having close contact with pigeons and

other birds, suggesting their food as a possible source of infection. These theories are borne out by the fact that Moniliae are extremely resistant to drying and to mild antiseptics.

Since the fungus is prevalent in the air, direct inhalation of contaminated dust or air may cuase its deposition in the lower respiratory tract. In this connection, the observations of Castellani[1] who found the organism in tea taster's nostrils, and who with Chalmers noted that guinea pigs into the nostrils of which tea dust was insufflated for months developed a bronchoalveolar moniliasis, are of interest. Haberfield, cited by deAlmeida and dos Santos[7], believes that the organism enters by inhalation, and writing to Lordy suggested the tonsils as portals of entry. DeAlmeida and dos Santos[7] claim that Moniliae may be disseminated by the blood stream as well as by lymph channels.

Ikeda[8] states that aspiration of the organism from the lesions in the upper air passages may cause their deposition in the lower bronchi and pulmonary alveoli. Three of his five patients suffered from chronic infection of the upper respiratory tract, and in one of the three, a species of Monilia was demonstrated in the hypertrophic antral mucosa removed by operation. Jacobson[9] believes that transmission of the organism from the gluteal anal fold may occur. A possible explanation is the reactivation of a dormant childhood infection.

Morphology. The yeast like cell predominates but a mycelium is produced in the lesions. Moniliae reproduce by budding and by the formation of a mycelium. The spores vary in size and morphology, but, in general, are large, round and oval. The mycelia are septate; lateral conidia are formed by budding near the joints of the hyphae, while terminal conidia are formed by budding and constriction at the ends of the hyphae. Globular chlamydospores with thick walls may be found. To a great extent, the morphology of the organism depends upon the type of cultural medium employed, but an aid to classification by a description of their characteristic growth on cornmeal has been offered by Martin et al.[10]

Cultural Characteristics. Moniliae grow rapidly at room or incubator temperature under aerobic conditions. On artificial media, especially on those containing dextrose, there appears in from 48 to 72 hours a creamy white growth of pasty consistency which emits a yeast-like odor. Microscopically, the colony consists of round or oval budding forms.

Anaerobic conditions and lack of fermentable carbohydrates seem necessary for mycelial formation. In old cultures fine mycelia extend out into the substrate, and no aerial mycelium is ever formed. Moniliae are best differentiated from true yeasts by a gelatin stab cultures. Monilia albicans throws out numerous fine lateral branches which gradually become shorter near the bottom of the stab, giving the growth the characteristic "inverted pine tree" appearance

first described by Ashford. In broth the growth usually consists of a flocculent accumulation of organisms which rapidly settles to the bottom of the tube.

There is considerable controversy regarding the carbohydrate reactions of Moniliae. Fineman (cited by Dodge[11]), working with seventeen strains supposedly Monilia albicans isolated from thrush, found the sugar reactions constant. Stovall and Bubolz[12] studied thirty-seven strains of Moniliae isolated from sputum and found all sugar reactions constant over a period of two years. According to Gay and his associates[13], and Jacobson[9], however, the fermentation of carbohydrates is not constant especially after subcultures.

At the present time the most practical and simple classification of Moniliae seems to be that advanced by Martin and his associates[10].

A Practical Classification of Moniliae

Species	Blood Agar Colonies	Mycelial growth on cornmeal	Aggt with M albicans antiserum	Path for rabbits	Sugar Reactions D	S	L	M	Milk
albicans	dull gray 1.5 mm smooth circular	tree-like chlamydosporeson tips of branches.Spherical spore clusters.Buds usually at ends of mycelial segments.	+	+	AG	A	–	AG	+
parapsilosis	pearly white,0.7 mm,smooth circular	produced with difficulty.No chlamydospores.Irregular spore clusters. Buds usually at ends of mycelial clusters.	+ –	–	AG	–	–	–	–
candida	gray-white 2mm.mycelial fringe	abundant mycelium chlamydospores,buds anywhere on mycelium.	+	+ in large doses	AG	AG	–	AG	–
krusei	dull gray white,0.2 -1.0 mm varying shape	naked threads with branching at wide intervals.No chlamydospores.Buds often in whirls at tips of mycelium	–	–	AG	–	–	–	–

A Practical Classification of Moniliae (Cont.)

mortifera	0.5 mm vary in shape	similar to parapsilosis	-	-	AG	AG	AG	-
stellatoidea	large, elevated central some with radiating arms	similar to albicans	-	-	AG	-	-	AG

D-dextrose
S-suchrose
L-lactose
M-maltose

Pathogenicity for Animals. The prevalent tendency is to regard only Monilia albicans as pathogenic. However, rabbits, guinea pigs, rats and mice are susceptible to virulent strains of Moniliae.

Castellani[1] found that the virulence of Moniliae varies as follows:

1. A few strains (generally isolated from the air) are avirulent. Injection by any route produces neither sickness nor death in the guinea pig or rabbit.
2. Certain strains are virulent and kill the rabbits and guinea pigs when inoculated intravenously or intrapulmonarily, but do not produce any evident pseudotubercular nodular conditions in the lungs.
3. Other strains when injected intrapulmonarily and at times intravenously produce a characteristic nodular condition in the lungs. When the animal is killed fifteen to twenty days after the inoculation, both lungs show numerous white nodules usually larger in the injected lung. These nodules may coalesce to form a staphyloid mass. The invasion of the non-inoculated lung is apparently via the bronchi which are often greatly distended and eroded. Histologically, the centers of the nodules are composed of masses of small leukocytes and polymorphonuclear cells which decrease in number peripherally. These are in turn surrounded by a ring of epithelial cells, some containing phagocytized white cells with a

few multinucleated giant cells. At times, the nodules show gross caseation due to the marked degeneration of the central cells in the nodules. In most cases there is some congestion but no pneumonia between the nodules. Thickening of the intima is present in the small arteries.

Castellani[1] maintains that the demonstration of the characteristic nodular condition in the lungs is essential for the establishment of the diagnosis of primary bronchopulmonary moniliasis. Other writers, however, contend that animal inoculation is not necessary when the sputum is repeatedly positive for Moniliae.

Grossi and Balog[5], using an emulsion of living organisms, found intrapulmonary injection to be the most efficacious method. Following inoculation of a virulent strain, they noted the marked similarity of the disease in rats to tuberculosis. Guinea pigs inoculated intracardiacly died from acute septicemia.

Kurotchkin and Chu[14] found that intrapulmonary inoculation of Monilia tropicalis, while it did not kill the animal in three to five weeks, produced extensive necrosis, obliteration of the pleural cavity and formation of a few nodules. Intra-abdominal and intravenous injection produced death by mycotic septicemia, forming small mycotic nodules in the lungs and other organs. In general, intravenous inoculation of a virulent strain produces general septicemia, and nodules may appear in various organs with and without simultaneous lung

involvement. Intraperitoneal inoculation may or may not succeed.

Stovall and Pessin[15] classified into three species more than 150 strains of yeastlike organisms associated with various diseases. Type 1, Monilia parapsilosis showed no pathogenicity even when injected in doses of three billions of organisms. Type 2, Monilia albicans, killed regularly in doses varying from twenty-five to seventy-five millions. Type 3, Monilia candida, killed only when large doses of six hundred millions of organisms were used. It was found that from five to fifteen times more cells of M. candida than of M. albicans were necessary to kill a rabbit on intravenous injection.

Serology

Agglutinative tests, according to most investigators, are unsatisfactory because the organisms show spontaneous agglutination. Steinfeld[25] concluded that the agglutinative reaction gave no significant information. Peruchena's[26] agglutinative experiments with normal and immune sera were negative, and in Parise's[27] case and that of Davis and Warren's[28] the organisms were not agglutinated by the patient's serum. Farah[3], however, found that the fungus gave a positive agglutinative reaction with his patient's serum.

Complement fixation reactions, using antigens prepared from cultures of the organisms, have been obtained by some investigators, notably Farah[3], Kurotchkin and Chu[15], Hoffstadt

and Lingenfelter[27], and Stone and Garrod[30]. Steinfeld[25] found this reaction of equivocal value.

The precipitin reaction appears to be a more simple and reliable test. A positive reaction was obtained by Kurotchkin and Chu[15], when the patient's serum was added to various extracts of monilial cells, control sera being negative. The procedure is also advocated by Stone and Garrod[30], and Davis and Warren[28].

Specific cutaneous allergy. Balog and Grossi[31] succeeded in eliciting a specific allergic cutaneous response in patients affected with pulmonary moniliasis, by means of an antigen consisting of a suspension of living Monilia. 0.1 c.c. of an emulsion prepared by adding 1 loopful of culture to 3 c.c. physiologic saline was injected endermally. With this living antigen, endermal inoculations were positive in all 18 of the patients with pulmonary moniliasis, and negative in all 53 normal healthy individuals or persons suffering from tuberculosis or other non-monilial disease. When an emulsion of heat killed fungus (1 hour at 65 degrees C.) was used, they obtained a non-specific reaction. Although endermal reactions were positive, scarification tests made simultaneously on the same patients were unsuccessful. In Steinfeld's[25] study of 15 cases associated with certain types of bronchial asthma, the results of the endermal reactions could not be interpreted.

Clinical Manifestations

The clinical symptoms of bronchopulmonary moniliasis

have been described by Castellani[1], Joekes and Simpson[16], Johns[17], Stovall[18], Warr[19], Ikeda[8] and others. Castellani distinguished three types: mild, intermediate and severe. The mild type, in which the patient is afebrile and has a good general condition, is characterized by a slight, but persistant cough which may last for weeks. Scanty mucopurulent sputum but no blood is produced. Physical examination of the chest is negative, or reveals only a few rales. A diagnosis of chronic bronchitis is usually made. The condition may last for weeks or months with frequent recurrences, may become cured spontaneously, or may progress into the more severe forms of the disease.

In the intermediate form, the symptoms resemble those of early pulmonary tuberculosis. Fever may be irregular or continuous. There is dyspnea and a severe cough, worse in the morning and at night. Sputum is mucopurulent and tenacious; hemoptysis may be present or absent. Recurrence is common, or there may be continued activity of the symptoms with intervals of quiescence. The usual diagnosis made is that of pulmonary tuberculosis, chronic bronchitis, bronchiectasis, or bronchial asthma.

The severe type of the disease presents two distinct clinical syndromes[8]. The patient with the mild or moderate form of the disease may suddenly show signs of acute pneumonia involving a wide area of one or both lungs. This may simulate a typical lobar or bronchopneumonia, or may represent a diffuse

inflammation of the lung, in which pathogenic micro-organisms play an important role, the infection at the same time serving as a fertile soil for the fungal growth. The patient is acutely ill, with a high temperature and every evidence of acute pulmonary infection. This condition, which lasts for a week or more, may subside completely or be followed by any of the complications of pneumonia.

The second type of the severe form of the disease may result from a complication of the preceding type or may represent a progressive low grade infection of long standing in which no etiologic agent except a pathogenic species of Monilia can be demonstrated. The course is prolonged and progressive with periods of exacerbation of the symptoms. Fever is hectic, there are night sweats, and emaciation with a gradual decrease in weight and strength. There are dyspnea and severe paroxsyms of coughing which ~~is~~ are worse at night. Sputum is increased in amount, is mucopurulent, tenacious, sometimes blood streaked, with a yeasty or sweetish odor. Secondary bacterial contamination may cause the sputum to become frankly purulent, copious and fetid. The physical signs of the chest are those of patchy condolidation, fibrosis and pleural thickening. There may be bronchial breathing, diminished or absent vocal fremitus, crepitation, and pleural friction rub. Often there are abscesses and cavities in the lower portions of the lungs. The whole clinical picture is extremely difficult to distinguish from that of an advanced pulmonary tuberculosis with

extensive cavitation. In advanced stages, a gradual embarrassment of the heart due to extensive fibrosis of the lungs may result in decompensation and death from the failure of the right side of the heart.

Prognosis is favorable in the mild cases, uncertain in the intermediate forms, and grave in the severe type which frequently constitutes a serious therapeutic problem.

X-ray studies are not remarkable and may show only the exaggerated linear markings usually observed in chronic bronchitis or bronchiectasis. During the acute febrile stage there may be a widespread shadow indicative of acute diffuse pneumonia, from which a diagnosis of lobar pneumonia is usually made. Chronic advanced stages may show irregular, mottled or feathery shadows with peribronchial thickening, fibrosis and intervening areas of emphysema or bronchiectasis cavities in a large portion of the lung. True cavities may be present. The differentiation of pulmonary moniliasis from chronic pulmonary tuberculosis is often difficult on the basis of X-ray studies alone.

However, Grossi and Balog[5] have pointed out some features which they believe to be of sufficient importance to direct suspicion to the true nature of the disease. They observed that the lesions in moniliasis were nodular in type, submiliary and fairly uniform in size - either discrete or confluent. The density of the lesions is not accentuated and hence there is a very hazy outline. Pleural involvement is not rare and

the bases are usually the seat of the infectious process. They found cylindrical bronchiectasis, with small nodular involvement in the peribronchial region, to be a frequent occurence.

There are no specific laboratory findings in this disease. The blood picture is not characteristic except for an eosinophilia, occasionally as high as 13 or 14%. Sedimentation rates are within normal limits.

Moniliasis and Tuberculosis

Frequently Moniliae and tubercle bacilli are found together in the sputum. Norris[20] in his survey of two tuberculosis sanitoria found yeasts in the sputum of 15% of the patients. This condition may be either a true double infection, or the Moniliae may only represent a saphrophyte. Grossi and Balog[5] mention three cases in which the symptoms clearly indicated the two diseases, and regarded the condition as a genuine moniliasis engrafted upon a tuberculous base. Many writers on the subject look upon the fungus only as a secondary invader when it is associated with tubercle bacilli. A large number even assume that it may be disregarded from a therapeutic standpoint. That the fungus, appearing in abundance, may antedate the tubercle bacilli in the sputum by months is not deemed proof of its priority as a causative agent. In general, these authors believe that the tubercle bacillus once it has appeared represents the primary infection and the Monilia is assigned a secondary rôle.

The opinion, however, that the fungus frequently causes the primary infection, has its supporters. Some writers feel that the ensuing pulmonary deterioration provides a more favorable soil for the subsequent lodging of the tubercle bacilli. In this connection Marett's observations are of interest. Ferguson[21] cites Marett as reporting that in the Channel Islands, monilial infection is as frequent as tuberculosis and that most tuberculous patients have a double infection. Marett found "Blastomycetes" alone in 40% of cases of suspected tuberculosis, "Blastomycetes" and tubercle bacilli in 40% of cases, and tubercle bacilli alone in only 20% of the cases. He believes that patients of the first class when left untreated soon become members of the second class which has a less hopeful outlook than that of the third class with tuberculosis alone. He finds that cases of true double infection do much better when the monilial condition is treated first. Balog and Grossi[31] agree with this opinion. Craik[22], who cites Marett's observations in his case report, says: "I think it probable that Colonel Marett has brought to light a truth unsuspected by his predecessors - that chronic blastomycetic bronchial catarrhs occur frequently and that they are the commonest precursors of tuberculosis in this country." (England)

Grossi and Balog[5] mention one important point of differentiation between the primary and secondary form of moniliasis accompanying tuberculosis. The primary cases always have

lesions at the base of the lung, while the secondary infections show lesions at or extending to the apex. A second point of differentiation is that in the secondary infection the fungus usually invades the mucous membrane of the mouth and pharynx. This is rare in primary moniliasis.

Pathology

Relatively few autopsy reports are available, and most of our knowledge of the pathology produced in this disease is based upon animal experimentation.

No lesions which may be construed as specific or peculiar to moniliasis have been described. However, there appears to be essential unanimity of opinion as to the cardinal changes present in the lungs which may partially explain the pathogenesis of this condition. Mendelson[23], in examining the lungs of a number of persons who suffered from this condition but who died of other disorders, described the pulmonary lesions as small tubercles which are in reality mycotic tumours standing out as very prominent white masses. This is the only record of early, non-fatal pulmonary lesions in man.

Microscopically the picture of the tubercle is that seen in other specific, granulomatous processes and consists of collections of leukocytes, epitheliod or giant cells, with or without a central necrosis. The periphery is usually composed of fibroblastic elements[9].

At autopsy, the lungs show areas of partial collapse and emphysema. The pleura may be greatly thickened and adherent,

and the areas of involvement feel rubbery. There are areas of pneumonic or nodular consolidation and fibrosis. Cavities and abscesses when present are usually in direct communication with the bronchi, representing dilated bronchi, bronchiectatic cavities or true focal necroses. The bronchi may be filled with tenacious mucopurulent sputum. The lesions are usually confined to the lower portions and bases of the lungs.

There may be generalized hyperemia throughout the affected pulmonary tissues, associated with a parenchymatous and interstitial edema of the alveolar epithelium and a narrowing of the alveolar tubules. The alveoli are distorted; many of them are dilated and contain a cellular exudate. Others are collapsed or obliterated by edema, exudation or fibrosis of the septal stroma, which may be transformed into a widespread area of fibrosis with foci of cellular infiltration of varying intensity and extent. Numerous air spaces which represent isolated alveoli may be found in these areas. The alveolar epithelium may show acute proliferation with areas of localized metaplasia[8].

Microscopically, there is intense inflammation of the bronchi, proliferative and suppurative. Some cases also show acute proliferation of the lining epithelium, while others reveal necrosis and ulceration of the superficial layer of the wall. The lumen often contains an acellular mucinous or albuminous coagulum, or an exudate of plasma cells and macrophages, sometimes with eosinophiles. There may be complete

obliteration of the alveoli and lumens of the smaller bronchi by the coagulum. There is usually a heavy zone of peribronchial fibrosis with an accumulation of plasma cells. The chronic localized abscesses are probably due to the necrosis and inflammation of the walls of the bronchi and bronchiectasis, but the abscesses may also be formed by the invasion of the Moniliae into the areas of unresolved pneumonia. The yeastlike cells, occasionally budding forms and rarely mycelial filaments, are found in the cellular exudate in the wall of the abscess or of inflamed bronchi. They may also be found in the regional bronchial lymph nodes where there is usually no local inflammatory reaction.

The character of the cellular exudate varies. In the uncomplicated primary infection, the chronic, low grade type of inflammation favors the production of the plasma cells and mononuclear leukocytes. Macrophages, sometimes with fat droplets, are present in the alveoli of the bordering areas. Eosinophils, and foreign body giant cells are sometimes found. Where cavities and large abscesses with secondary invaders have formed, polymorphonuclear neutrophils are abundant.

The involved areas also show changes in and about the blood vessels. Small arteries may have diffuse edema and thickening of the walls, a heavy perivascular zone of round cell infiltration with fibrosis. The general picture is that of a miliary nodular periarteritis. The larger areas, however, show a well defined subintimal swelling and connective tissue proliferation

often to obliteration, producing a high degree of chronic endarteritis.

Diagnosis

Bronchopulmonary moniliasis may simulate any of the bronchopulmonary diseases, and clinical diagnosis of this disease is practically impossible. Differentiation from tuberculosis is as difficult as it is important from an economic and therapeutic standpoint.

A positive diagnosis of moniliasis is justified only when a pathogenic species of Monilia is constantly found in the sputum in large numbers, and when the organism disappears coincident with the patient's clinical improvement. It goes without saying that the sputum must be obtained directly from the lungs, taking every precaution to avoid contamination. For this purpose, a single specimen expectorated after a thorough rinsing of the mouth with sterile saline or some mild antiseptic, is essential. The sputum should be examined directly and cultured immediately to prevent air contamination. The other methods of diagnosis, such as serologic techniques and skin tests, are still in an experimental state, and can not be substituted for the identification and classification of the organism.

The particular species of Monilia involved can be determined only by morphology and cultural reactions. A more simplified technique than that of Castellani's seems to be sufficient to identify the organism on the basis of biochemical

reactions on carbohydrate media, since the present tendency seems to be to recognize fewer species. Jacobson[9] summarized his conclusion as follows: "The difficulty lies not merely in terminology but also in the methods of identification, since the organism may show a difference in morphologic behavior under different artificial conditions."

It is essential to remember that the mere presence of a Monilia in the sputum should never be considered sufficient to establish a diagnosis of broncho-moniliasis. Animal inoculation should always be employed in order to determine the pathogenicity of the species isolated. When a Monilia is found in sputum collected with all due precautions to avoid external contamination and examined at one, there are three possibilities:

1. The Monilia, though present in the expectoration, is avirulent and non-pathogenic, and lives saphrophytically in the bronchi.
2. The Monilia, though virulent, may be present in the sputum as a secondary invader.
3. The Monilia is the real cause of the broncho-pulmonary condition.

The dictum that the distinction between primary and secondary bronchomoniliasis lies in whether or not the organism is capable of producing the pseudotuberculous nodules in the lungs must be accepted with reservation. In differential diagnosis from tuberculosis, guinea pig inoculation should never be

neglected. X-ray examination is important even though it serves only to rule out pulmonary carcinoma. Frequently only the bases of the lungs are involved in monilial infections, the apices remaining clear. However the roentgenogram may correspond to that of tuberculosis in any of its stages.

Treatment

Monilial infections imply a soil rendered susceptible by a break in some point in the immunity chain. Any effective treatment must involve a thorough examination of the patient from the standpoint of diet, environment, elimination, endocrines, and blood chemistry. Jacobson[9] mentions two points of possible importance in disturbed carbohydrate metabolism, and autointoxication from the gastro-intestinal tract which can often by corrected with good results.

Treatment of pulmonary moniliasis, as that of other parasitic diseases, must consist of an effort to destroy the causative organisms when possible, or to so alter their environment as to hamper their growth and nutrition. Potassium iodide has produced such beneficial effects in mild and intermediate cases that it has come to be regarded as the specific. Potassium iodide should be given in doses of four to fifteen grams t.i.d. in milk or water, and continued for some weeks after all symptoms have subsided. Castellani[32] advised creosote, glycerophosphates and balsaica in addition. In severe cases, potassium iodide seems to be of little if any value. Lipiodal injected intracheally deserves further trial, and may be com-

bined with intramuscular injections. Jacobson[9] recommends tincture of iodine in doses of five to one hundred drops t.i.d. and sodium iodide intravenously. Norris[20] has also used sodium and potassium iodide intravenously with good results.

A number of therapeutic agents have been tried by other authors with varying success. Grossi and Balog[5] believe that insulin is of value even in cases without glycosuria. Stovall and Greeley[18] obtained improvement in their one case treated with intravenous gentian violet. Craik[22] treated his patient sucessfully with alkalis, potassium iodide and adrenalin. Chyurlia[33] reported a chronic case from Venice in which iodides, alkalies by mouth, ultraviolet rays and Steinfeld's autovaccine method produced good results. Farah[3] advocated pneumosan injections- 2 c.c. of 40% iodized poppy oil injected intramuscularly (gluteal region) on alternate days.

Howe and Schmidt[38] reported satisfactory results in ten cases of bronchomycoses with small doses of roentgen rays, but they did not state the particular kind of yeast-like fungus involved.

Vaccine treatment has been used with varying success. Balog and Grossi[31] used the same vaccines as in the skin test. The initial dose was 0.1 c.c. and each succeeding dose, given only after all symptoms had subsided, was increased by 0.1 c.c. In their series of cases, healing was effected in most cases in a short time, and the remainder were greatly improved.

They noted that monilial vaccine therapy always acted

gently, desensitization taking place during the treatment. According to these authors, vaccine treatment is the only therapy which restores the myocardium after injury by the monilial toxins.

Kotkis, Wachowiak and Fleisher[35] saw complete disappearance of symptoms with the use of autogenous vaccines in one case, and great improvement in a second before it passed out of control. In a series of sixteen cases which Pijper[36] treated only with autogenous vaccines, the doses ranging from fifty to two thousand million cells, very good results were obtained in three cases, distinct improvement in three others, and no change in the remaining ten. In Steinfeld's[25] fifteen cases, doses ranging from 0.1 to 1.0 c.c. of a vaccine prepared from heat killed organisms seemed efficacious. Sur[37] reported a case treated successfully with an emulsion of a twenty-four hour culture of organism in normal saline made up to contain one hundred million organisms in 1.0 c.c. Doses of twenty, forty, seventy and one hundred million organisms were given at two, three and four day intervals.

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Coccidioidal Granuloma

The term coccidioidal granuloma is used to describe a disease caused by Coccidioides immitis. Although it has been known for more than forty years, interest in its study has been recently revived due to the fact that more cases have been recognized during the past few years.

The condition may be localized and benign, or systemic, malignant and rapidly fatal. It is protean in its clinical manifestations, more frequently mimicking tuberculosis than other fungal disorders. Pathologically, the process is granulomatous in character, closely resembling the picture observed in other members of the group known as infectious granuloma.

The general conceptions of the disease have been gradually changing from the time it was regarded rare and 98% fatal, until the present when thirty new cases, with a mortality rate of 49.7% are reported each year to the California Department of Public Health. Recently it has been realized that coccidioidal granuloma is in reality the terminal stage of an acute illness characterized by bronchopneumonia and usually by erythema nodosum.

The number of articles is great in proportion to the number of cases in this country. The reports appearing in medical journals have dealt almost exclusively with cases in North and South America. Methods of therapy, in the main unsuccessful, have been suggested, and careful morphological studies of the

organism have been made by some authors.

History

In 1893, a middle aged Portugese entered the City and County Hospital in San Francisco, suffering from a chronic ulceration on the back of his neck of one year's duration. After the usual methods of treatment for simple ulcer had failed, the purulent discharge was examined microscopically and large numbers of a spherical organism with highly refractile capsules and endospores were seen. A great variety of therapeutic agents was tried without success, and the disease spread rapidly with general involvement. The disease was reproduced in a dog, which completely recovered after excision of the ulcer, and subsequently lived for many years.

When Dr. Rixford presented this case before a meeting of the California Academy of Medicine, Dr. W. S. Thorne[2] stated that he had a similar case. Attention was then called to a report in the literature by Wernicke and Posadas[3] in Buenos Aires.

Drs. Rixford and Thorne thought the organisms were Protozoa because of the resemblance to Coccidia. The material from these cases was sent to Dr. W. H. Welch at Johns Hopkins who doubted that the organisms were Protozoa, and who turned it over to Drs. Gilchrist and Styles who gave them the name Coccidioides, resembling Coccidia. The organism from the first case was called C. immitis, and that from the second, C. pyogenes.

Both patients died after short periods, and since they were Portugese, the disease was thought to have been imported from the tropics. However, when it was learned that both had lived in the San Joaquin Valley, its origin was believed to be nearer home.

Despite diligent search, the next case was not reported until 1900 by Dr. Rachael Ash. It was material from this case that enabled Dr. Ophuls[4] to isolate the organism in pure culture.

In 1930, at a meeting of the California Medical Association, Dr. Weidman showed slides from a case in Chicago. This organism was of the form of Dr. Thorne's case (C. pyogenes), and thirty-six years had elapsed before this form was seen again. However, the lesions in this case were confined to the skin.

Since up to July first, 1936, 450 cases had been reported, most of them originating in the lung and with a high mortality, the disease has attracted widespread attention and was made reportable in 1928.

Mycology

Morphology: There are at present recognized two species of Coccidiodes: C. immitis, the etiologic agent of the disease in North America and Argentina; and C. brasilensis, the cause of the disease in Brazil. The latter chiefly affects the buccal cavity and the gastro-intestinal tract with marked adenopathy. Of the 257 reported cases of this type of disease, only fifteen percent showed pulmonary lesions. This discussion

will be limited to C. immitis.

C. immitis appears in tissues and exudates as a spherical, double contoured capsule, varying in size from five to sixty microns. The mature spherules in the tissues average thirty microns, the younger forms being much smaller, and the endosporulating mature forms much larger. The outer wall is a thick, hyaline capsule sometimes covered with spines or prickles. Reproduction occurs by endosporulation, and the development of hyphae is only characteristic of the saphrophytic growth, never being observed in the animal body. The organism is Gram negative, and the capsule is acid fast.

Cultural characteristics: Coccidioides grows well upon all kinds of culture media. Most luxuriant growth is obtained on Saboroud's, glucose, hormone, or cystine blood agar. There is less abundant growth on synthetic media. The organism is not overgrown by bacteria.

In broth, a pellicle is sometimes formed, but usually the liquid is clear with white fluffy balls of fine branching mycelium at the bottom of the tube.

On agar plates, large spreading colonies (6 cm. or more) are formed. They are white to cream colored with loose aerial mycelium. Maximum development occurs at three weeks.

On agar slants, the growth first appears as small, white nodules made up of branching hyphae which soon coalesce to form a fluffy, white growth covering the whole surface of the medium and anchored by fine mycelia.

Glucose, mannite, maltose, saccharose and lactose are not fermented. Blood agar is hemolyzed; litmus milk is peptonized and decolorized in four days; gelatin is liquified; and Loeffler's blood serum is liquified and proteolized.

The optimal temperature is thirty degrees centigrade with more abundant growth at thirty-seven degrees centigrade. No growth occurs at higher temperatures. The organism is inhibited at refrigerator temperature, but grows later. The incubation period is from two to ten days, average four.

Cultures observed microscopically show tangled mycelia made up of septate hyphae. There is clubbing of the terminal hyphae. Old cultures break up into arthrospores and fusiform chlamydospores which have a double wall similar to that of the capsules in tissues.

Pathogenicity for animals: Most animals are susceptible to C. immitis. In guinea pigs and rabbits, intravenous, intraabdominal and subcutaneous injections lead to a generalized infection.

Life Cycle

C. immitis has a double life cycle which was the cause of confusion in its early study. In 1894, the only men equipped to do bacteriologic work in San Francisco were Drs. Mouser and Montgomery. Mouser's cultures failed to grow, and Montgomery's grew into the mold now recognized as typical. Believing this a contaminant, however, he threw the cultures away. It was not

until 1900 that Dr. Ophuls[4] secured the material that enabled him to discover that the organism appeared as a mold on culture media and developed its spherical forms within the body.

The first or vegetative phase is the development of the hyphae to form the mold growth. This was first described by Ophuls[4] who studied the development of individual spherules suspended in hanging drop preparations.

> "The thick membrane which surrounds the latter (spherule) becomes very thin in one place and begins to evaginate over the bud from the enclosed protoplasm. These buds soon assume the form of coarse, more or less cylindrical bands which are either straight or somewhat wavy. At first the protoplasm forms one continuous mass in the main body (of the spherule) and buds, but after a while septa appear at various places in the buds, and sometimes particles are formed between the buds and the main body."[4]

Wolbach[5] stated that he believed that the organism's mycelia sprout from the capsule, but MacNeal and Taylor[6] and Chope[7] agree with Ophuls that the mycelia begin as evaginations of the protoplasm thru the capsule. Chope[7] also observed instances in which the sprouting filaments originated from the endospores in pus before they had been released from the spherule. In this case the pus had been evacuated as hypha formation has never been seen in animals and is as specifically limited to the growth on medium outside the body as reproduction by endosporulation is restricted to development within the tissues.

Ophuls[4] pointed out that all spherules do not sprout hypha, but there are apparently no features to distinguish a spherule which will form hypha from one that will not. Ahlfeldt[39]

described minute bodies in the compartments of mycelia from which the spherules are formed which suggested to her sexual elements and the possibility of bisexual life, but she did not observe conjugation and her contention has not been supported by other authors.

Chlamydospore formation is observed in old cultures. The aerial hyphae first divide into segments by firm partition followed by the development of thickened capsules. Finally the now brittle hyphae separate by fragmentation. When the chlamydospores are liberated, they occur singly or in groups which remain attached to each other by the persisting portions of the hyphae which connect them. If these chlamydospores are now transferred to fresh culture media, mycelia promptly sprout with the formation of new colonies.

The second or parasitic phase of development is the formation of the spherules in the tissues. This has been described by several authors. Recently Chope[7] has checked this process before attempting to ascertain the type of tissue reactions produced. There has been some difference of opinion as to whether the spherules develop only from chlamydospores (Ophuls[4] stated that the fungus is not infective unless chlamydospores are present) or whether the undifferentiated hyphae are spherulogenic (Wolbach[5]). Chope[7] approached the problem by preparing cultures from infectious pus and from a stock culture and injecting them into guinea pig testicles after 2, 4, and 7 days incubation. One animal was killed every

four hours. The 2 day culture had no chlamydospores, the four day culture showed hyphae in early stages of differentiation, and the 7 day culture showed well formed chlamydospores, Chope[7] found that spherules were formed from mycelia containing no chlamydospores but after a longer time than when mycelia with chlamydospores were used, The author did not mention whether the undifferentiated mycelia went thru the stage of chlamydospore production before forming spherules. A 2 day stock culture produced spherules more quickly than did a 2 day culture from pus.

The sequel of events occuring after the injection of the fungus was found to differ only in detail from that described by Ophuls[4] and Wolbach[5]. Chope's experiments showed a shorter time for the completion of the intra- tissue cycle, probably due to the fact that his inoculum was standardized to the extent that only 8 and 10 day cultures were used. These cultures contained mature chlamydospores since it has been found that spherule formation occured more promptly when the mycelia contained chlamydospores. After the injection of the mycelial suspension, the outline of the hypha was intact on the third day, but some of the chlamydospores were somewhat rounded with a well defined outer capsule. At 44 hours some of the chlamydospores were well rounded although still connected together, and at 60 hours the spherules were well developed - about 30 mm - as large as the immature spherules found in exudates. By 72 hours some of the spherules were filled with endospores

and in 96 hours some of them had burst showing the manner in which the endospores were liberated and how the envelop was formed.

In anaerobic cultures Chope[7] saw spherical enlargements of the chlamydospores in segments of the hyphae. In size and character they resembled the partially matured spherules seen free in pus, but were not separated from the mycelial growth, and secondary formation of endospores in them was not observed. On one occasion he noted a similar type of development in the hypha of a spherule which had sporuted in pus that had been left standing in an open vessel at room temperature. Smith,[8] however, has stated that these spherules die after five minutes exposure to air. MacNeal and Taylor[6] observed one such spherule formation in an anaerobic culture, but since usually no spherule formation occured in anaerobic cultures, this does not appear to depend wholely on low oxygen tension.

Occasionally endosporulating spherules with a different appearance have been seen in pus and tissues. Sometimes the spherules have large central vacuoles with the endospores arranged peripherally. Rixford[1] thought they represented a new species- C. pyogenes- which was more virulent than C. immitis. Fonseca[9] gave the name Pseudococcidioides Mazzai to a similar form described by Mazzai. De Almeida,[1] in his discussion of it, observed that in the formation of spores radiating openings appeared in the protoplasm which was divided into cones. New divisons then appeared parallel to the membrane

of the cell which cut the original cell perpendicularly making the appearance of a polyhedral cell. Since these forms occur side by side with the regular form, apparently having developed from the same chlamydospores, they are not different species but are probably due to some unexplained environmental factor.

Another form described by Posadas[3] and later by Ophuls[4] is the development of a cluster of smaller spherules within the capsule of an unruptured mother spherule. Posadas[3] described them as vegetative forms beginning with the appearance of the parasite in the protoplasm which is going to divide of clear, small spherules which are slowly formed into adult endocysts that are retained within the mother cyst. Ophuls[4] disagreed that they indicated a different type, saying that they signified only an especially rapid development. Chope[7] saw similar forms in sections of tissues - on one occasion in a section of bovine coccidioidal granuloma, and in a testicle of a guinea pig 8 days after inoculation.

Prickles on the capsules of a few spherules was first noted by Rixford. Ophuls[4] found them almost constant on the outside of sporulating forms. Ahlfeldt[39] noted them only on the adult forms when ready to liberate the young forms. Chope's[7] observations coincide more closely with those of Wolbach. In one series of animals inoculated intra-abdominally, epididymal abscesses (in the depths of a collection of pus cells only) showed minute circular bodies the size of an erythrocyte completely surrounded by fine radiating spicules producing a burr-

like appearance. In the same section, however, large, non-sporulating spherules were seen which did not show spicule formation. From the fact that these prickle forms only developed around the margins of pus, it is possible that they are due to insufficient aeration or to toxins caused by the accumulation of pus. Chope[7] also observed prickle formation in some chains of chlamydospores which had not separated 60 hours after injection. Prickle formation, however, is not ordinarily observed on endosporulating spherule, being present only on rare occasions.

Serology

The development of satisfactory serologic and allergic reactions for the diagnosis of coccidioidal granuloma has been the aim of several writers.

Agglutinative Reaction: Results from this reaction have been uniformly negative among many authors who have used both animal and human blood.

Precipitative Reaction: Cooke[11] demonstrated precipitins in serum from cases of coccidioidal granuloma using as antigen an extract of dried culture of the organism. These precipitins were apparently specific since they could not be demonstrated in normal serum using the same antigen, or in specific immune serum tested with blastomycin. Templeton[12] and MacDonald[15] obtained positive precipitative reactions, while Cummins and Saunders,[13] and Smith[8] failed to demonstrate precipitins in

serum from patients with coccidioidal granuloma.

Complement Fixation: Davis[14] obtained complement fixation using as antigen a concentrated culture. Chipman and Templeton[12] using a Berkefeld filtrate and Kolner's technique obtained a positive reaction up to 1:2,200. Smith[8] observed a strongly positive reaction using coccidiodin as antigen with blood serum from cases of coccidioidal granuloma. Cummins and Saunders[13] and MacDonald[15] did not concur with the above authors.

Endermal Reactions

The results of skin tests have been more encouraging than those of the serologic reactions.

In animals, Giltner[16] obtained a negative subcutaneous reaction using a product of the organism similar to tuberculin. D'Andrea[17] found that guinea pigs could be sensitized to a broth culture filtrate of killed, dried mycelia of C. immitis. He believed the reaction was probably allergic. Traum and Harrington[18] called attention to the close relation in animals between coccidioidin and tuberculin reactions, since these investigators obtained some positive tuberculin reactions in animals infected with C. immitis. This reaction was not constant. Cummins and Saunders[13] obtained a stronger cutaneous reaction with an unheated broth filtrate than with one heated at seventy degrees centigrade. They concluded that C. immitis does not produce a diffusible toxin.

Positive endermal reactions have been obtained by many

authors. Davis,[14] using an homologous suspension of killed organisms, obtained a much more severe reaction than with sporotrichin, blastomycin, and agar.

Jacobson[19] prepared an antigen from a Berkefeld filtrate of a ten day's culture of the organism. Following preliminary studies on goats and guinea pigs to determine toxicity, he injected 0.3 cc. endermally. Patients with coccidioidal granuloma showed erythema in twelve hours with a peripheral enlargement in twenty-four to thirty-six hours. There was an oval or semi-oval inflamed area, six by eight centimeters, intensely red, markedly swollen and tender. In addition to the local reaction of margination, infiltration and warmth, discharging abscesses and sinuses increased in flow, and some tumours softened and discharged. Jacobson concluded that this organism produces an extra-cellular substance which is non-toxic to persons free from the disease but which produces a characteristic local reaction around the site of injection in persons with coccidioidal granuloma. He believed that the allergic cutaneous reaction was probably due to the extra-cellular products of the organism, the reaction being similar to that of tuberculin and luetin.

The above results were duplicated by Smith,[8] Chipman and Templeton,[12] Hirsch[20], and Miller.[21] The most thorough study of the endermal reaction was carried out in 1938 by Hurwitz, Young and Eddie[22] on 449 hospitalized patients. Their antigen was standardized so that 1 c.c. contained 0.1 mg of an old

broth culture of mycelia and spores suspended in saline. 0.1 c.c. was injected and normal saline used as a control. Reactions were read at 24 and 48 hours and an area of induration 5 mm or more in 48 hours was considered positive. 12 patients with coccidioides disease reacted positively, but positives were obtained in other diseases, notably tuberculosis (27.5% positive). A higher percentage of positive reactions was observed among the residents of the San Joaquin Valley. The authors believe that a diminution of concentration may prevent some of the false positives.

An interesting phenomenon was found by Dickson[23] (1938) who observed that Jacobson's dose of 0.3 c.c. was much too strong for valley fever, producing intense necrosis and edema in cases of acute involvement. Dickson could produce a well marked reaction sometimes with vesicle formation, in his cases of primary involvement with 0.1 c.c. of 1:1000 dilution whereas 0.1 c.c. of a 1:10 dilution was necessary for the cases of coccidioidal granuloma. This corresponds to the experience of Wallgren[24] (1938) who found that among children with erythema nodosum accompanying primary tuberculosis, the sensitivity to tuberculin may be so marked as to cause a reaction to 0.000001 mg. whereas only 3 children out of 321 without erythema nodosum reacted to 0.001 mg.

Epidemiology

Geographical Distribution: Coccidioidal granuloma is apparently endemic in the San Joaquin Valley, but cases have been reported from elsewhere in the United States, Canada, Brazil, Argentina, and Italy.

Up to July first, 1936, there had been reported 450 cases with 234 deaths with a concentration of 66.8% in central and southern California. Between January first, 1936 and May, 1937, 354 cases of valley fever were seen. Approximately forty cases have been reported from the rest of the United States, most of them from the west. The states represented include Texas (5 cases), Louisiana (3 cases), Pennsylvania (3 cases), New Mexico, Arizona, Washington, Colorado, Kansas, Nebraska, Missouri, Illinois and South Carolina each with one case. Fourteen cases have been reported from South America, two from Italy and one in Canada.

The indication that most of these cases have come from central and southern California is probably due to the fact that many of the early histories did not give addresses and hence were charged to the locality in which the diagnosis was made. This accounts for many of the San Francisco reports, together with the fact that most of the early work was done in this medical center. Another difficulty in allocating cases has been lack of knowledge concerning the incubation period. It hardly seems logical to charge cases to the San Joaquin

Valley when the patients had merely passed through it, or had lived there for a short period some time in their lives.

That the impression of its geographical limitation does not bear careful investigation is apparent to anyone who finds it hard to believe that an organism which apparently thrives luxuriously on animal tissue, would confine itself to one or two persons in such large areas of population as Texas and Illinois without manifesting its activities in later years.

Apart from increased alertness in diagnosis, there appears to be an actual increase in the number of cases reported, although it has been noted that when the medical profession becomes interested in a particular disease, its morbidity rate rises.

Age and Sex: 85% of the cases occurred in males, 13.3% were in females, and in five of the cases, the sex was not mentioned. A number of cases occured in children, one in a three months old infant, and ten in the age group between one and four years. However, the majority fall in the higher age groups, especially in that between twenty-five and fifty-five years, and incidence of 61%.

Race: Practically all races are affected, the highest incidences being among Americans (30%) and Mexicans (21%). The number of cases reported among the Filipinos has increased within the last five years to the present figure of 14.9%. Sorsky,[25] among other writers, has noted the apparent predisposition of Mexicans to this disease. A more conservative

viewpoint is to regard it as a reflection upon the environmental and occupational status of this group rather than a true racial predisposition. Cases have also been reported among Negroes, Japanese, Portugese, Hindus, East Indians and Malayans.

Occupation: 65.5% of the cases were found in groups associated with outdoor work, especially those involving contact with soil, vegetables and animals. This bears out the epidemiologic theory that the disease is soil borne. Two cases have been known laboratory infections. Nearly all trades and professions are represented among the remaining cases.

Incidence and Geographical Distribution in Animals: Since Giltner[16] in 1918 published the first report of Coccidioides in lesions of slaughtered cattle, twenty cases have been reported as follows: Beck[26] (1929) six cases in cattle and one in sheep; Traum[18] (1929) two cases in cattle; and Beck, Traum, and Harrington[18] (1930) ten cases in cattle.

The geographical distribution of Coccidioides in animals has been found to parallel that of humans with the concentration in central and southern California. Studies of the bronchial and mediastinal lymph glands from slaughtered animals were negative in Humboldt County where no human cases have been reported.

Occurence in Nature: The high incidence of cases among agricultural workers and laboring classes has suggested that soil and vegetation offer the most probable source of infection. Most experiments to demonstrate mycelia in nature have been

fruitless, and Coccidioides had never been observed in nature until isolated from soil secured in an endemic area by Stewart and Myer.[27]

Transmission: Epidemiologic evidence has not favored the belief in man to man or animal to man transmission. Studies of other possible modes of infection such as insect bite have been negative. Ophuls[4] was unable to inoculate new lesions in the sound skin of patients suffering from the disease. Spores in pus have been found to die after exposure to the air for five minutes and probably can not cause infection unless they immediately find a satisfactory lodging place in an abrasion or mucous membrane. Infection probably takes place more readily by means of culture laden material such as vegetable matter which supports a growth capable of being inhaled or inoculated.

Mode of Infection: Since Coccidioides has been chiefly reported in the San Joaquin Valley and has been found in cattle and sheep as well as in man, there has been much interest in how the infection was acquired. The two theories most often advanced have been by means of a skin abrasion or through the respiratory tract.

A few cases have been reported where infection has occurred at the site of a break in the skin such as that caused by a cactus spine, but, in the main, most reports have lacked the history of such a trauma. However, this belief has been supported by the isolation from the soil of the fungus.

The theory that the infection follows the inhalation of chlamydospores has necessitated the disregarding of the organism as it appears in the tissues, and has made it necessary to consider some vegetative phase of the fungal growth as the infective agent. The investigators who have worked with Coccioides have recognized that the mode of reproduction is through the chlamydospores and it has seemed possible to some people that the chlamydospores of the vegetative phase might be the mode of infection since they are so light they can easily be inhaled. Unfortunately, the chlamydospores have not been studied ordinarily by the clinician who sees only the patient with the parasitic phase.

Proof that the inhalation of chlamydospores may cause coccidioidal infection has been established by two laboratory cases. Students commencing work on the fungus inadvertently removed the covers of old plate cultures with the rise of a fine cloud. Nine days later, both became ill with a symptom complex since realized to be common in the San Joaquin Valley.

Incubation Period: The cases cited above have shown that the clinical symptoms were manifested in nine days after exposure to the organism. Intraabdominal injection of C. immitis in guinea pigs gave rise to signs and symptoms of the disease in from ten to fourteen days. The period of ten days, according to Ahlfeldt[39], corresponds to the number of days required for the formation of spores and their consequent systemic dissemination.

However, the fact that Chope[7] found that mycelia without

chlamydospores would produce spherule in animals, may alter our conceptions of the method and incubation period of the infection.

Clinical Manifestations

For convenience, three types of coccidiodal disease may be distinguished. A. Paracoccidiodes - the Brazilian form of the disease - affects chiefly the mouth and gastro-intestinal tract with adenopathy. Of the 257 cases reported, C. immitis was the eticlogic agent in only two. Only 15% of these 255 cases showed pulmonary involvement - always decidedly secondary. B. Desert or valley fever - the acute stage of an illness in the San Joaquin Valley which in some instances progresses to a generalized granuloma. C. Coccidioidal granuloma - a generalized disease involving mainly the respiratory tract, osseous system and the skin.

Dickson[23] has suggested the name "coccidiomycosis" for the disease - primary for the acute, initial infection, and progressive or secondary for the coccidioidal granuloma. The latter may be subdivided to indicate the regional distribution of the lesions.

Valley Fever

Within the last few years investigators in reporting cases noted that the initial symptoms were often a severe "cold", "grippe", "flu", "pneumonia" or more accurately a broncho-pneumonia accompanied often by erythema nodosum.

Investigation has shown that a symptom complex has been

found so common in the San Joaquin Valley that it is popularly known as desert or valley fever. There is a characteristic seasonal incidence; all ages and sexes are affected. The duration of the disease is from three to six weeks and recovery without complications is usual. Dickson[23] stated in a recent report:

"In a questionnaire sent to the practicing physicians of the San Joaquin Valley, 75 physicians reported that they had seen 354 patients with valley fever or erythema nodosum between January 1, 1936 and May, 1937 of whom 353 recovered without complications and one had died of coccidioidal meningitis."

The patient usually describes the onset of the acute illness as a bad cold or flu. Sometimes there are localized pains around the chest and the patient complains of pleursy - often so severe that the chest is taped. There are occasionally indefinite gastro-intestinal symptoms and frequently a sore throat or mild tonsillitis. Conjunctivitis has been noted with bulbar hyperemia and rarely phylctenulae. A rapid loss of weight of as much as 15 - 20 pounds may be seen. Fever may begin at the onset or be delayed until the fourth or fifth day, ranging from 100 to 105 degrees F. The incidence of early chills or sweats is not high.

Early bronchitis is common either with unproductive cough or varying amounts of mucopurulent sputum sometimes blood streaked. Usually the patient feels better after a short time and thinks he is recovering until from 8 to 15 days after the onset, erythema nodosum develops. It is usually at this stage that a physician is consulted.

The nodules of erythema nodosum may be localized on the shins or multiforme, occurring on the thighs, buttocks, arms, upperpart of the chest and scalp. They are fiery red, very tender and painful but do not fluctuate or suppurate. Within 48 to 72 hours the nodules change from fiery red to purplish and fade. They have usually disappeared in from 4 to 5 days except for a brownish pigmentation of the skin which may persist for several weeks after the disappearance of the tenderness and swelling. There are rarely re-occurring attacks of erythema nodosum during the period of a single illness. It is only after the occurrence of the "bumps" that the disease is called desert or valley fever.

Pathology: X-rays taken during an acute attack show dense shadows in the hilar regions indicating an enlargement of the hilar glands. Radiating from the hilar regions and distributed more widely through the lung are densities indicating parenchymatous involvement in various parts of the lung which may occur in all the lobes. In most of the reported cases, the first examination has led to the roentgenologic diagnosis of tuberculosis, but as time went on the areas of increased density gradually cleared until in a few weeks the lung appeared entirely clear and the roentgenologist stated the conclusion that the condition could not have been tuberculosis because the lungs cleared so rapidly. Occasionally a patient with such pulmonary shadows has been sent to a sanitorium when it was impossible to prove tuberculosis by bacteriologic or immunologic tests.

Laboratory findings: The urine is usually no different than in other febrile conditions. Leukocytes are normal or increased with a maximum of 15,000. Eosinophils may be associated with erythema nodosum and Dickson reported one case with 16% on the 8th day of the illness. Sedimentation rates on three patients were 31, 32, and 45 mm. in 60 minutes.

The sputum from these cases is usually negative for acid fast bacill although the two conditions are known to exist together. Usually the typical spherules of Coccidioides are found. Cultures produce the typical mold growth which is pathogenic for guinea pigs. It is not known how long the fungus may be found in the sputum or how early it appears, but it may disappear before the sputum production ceases.

Coccidioidal Granuloma

The initial symptoms vary greatly with the localization of lesions. However the most frequent is respiratory attack described as "pneumonia", "flu", or "tuberculosis" followed in a few weeks by rheumatic pains. adenopathy, abscesses and lesions of bone and skin. There are usually fever, malaise, cough, and sputum which may be blood tinged. True hemoptysis is rare. The pulmonary symptoms may disappear and the disease become chronic, remaining localized for years. However, the disease may run a rapid course even before somatic lesions are apparent and lead to death. In other cases, there is a rapid dissemination of the organism causing severe toxemia, prostration and death.

An outstanding characteristic of coccidioidal granuloma in its mode of onset, early clinical course and pathology is its mimicry of tuberculosis.

Physical examination: In most moderate and far advanced cases, the patient is cachectic, anemic and emaciated. Chest findings are comparable to those found in tuberculosis, but careful palpation of the chest may reveal either small sub-cutaneous abscesses or actual invasion of the sternum and ribs by the organism.

Laboratory findings: The temperature may reach 105 degrees, but the fever curve is of no diagnostic value. The urine resembles that found in other febrile conditions. There may be normal hemoglobin and red cell count, or a moderate anemia. The leukocyte count varies from normal to an absolute and relative increase in polymorphonuclear neutrophiles. Cerebro-spinal fluid is indistinguishable from that of tuberculosis except that acid-fast bacilli can not be demonstrated. Blood cultures are usually negative, but have occasionally been positive in advanced cases. The organism has not been recovered from the urine or feces. The sputum usually contains the fungus.

X-ray Studies: Carter[28] examined 37 cases all of which except one showed involvement. Two others which were negative later had positive films. In a general way the thoracic pathology on the X-ray plates resembles that of tuberculosis since both diseases produce granulomatous lesions of the lungs.

The outstanding features of the coccidioidal chests were:

1. High incidence of mediastinal involvement with right mediastinum usually the broadest (17 cases).
2. Miliary lesions (19 cases). Questionable or negative in remainder.
3. Hilar thickening - uni-or bi-lateral with a right sided predominance (31 cases).
4. Parenchymatous infiltration (32 cases).

There may be a rapidly migrating type of pneumonia with clearing in one lung and extension in the other. Localized areas of atalectasis approaching a massive collapse may be seen.

The lesions differed from those of tuberculosis in that fibrosis and cavitation were rare; they were characterized by a vagueness and softness of definition considered due to a tendency of the exudate to shift. Distinction from blastomycosis is difficult, but the latter usually shows a higher incidence of fibrosis, massive consolidation, pleural involvement and a lower incidence of mediastinal adenopathy and miliary lesions. Pulmonary involvement conforms to a type not seen in most cases of tuberculosis and is suggested when in combination with other symptoms, since it is seldom seen alone. The coccidioidal lesions develop at times much more rapidly than do those of tuberculosis.

Pathology: This was first described by Ophuls[4] as: "submiliary, miliary, or larger nodules which resemble tuberculosis very closely. These nodules may caseate. Later the

caseous material may liquify and cavities containing pus-like material may be produced in this way, or in other cases there may be suppuration from the beginning, sometimes of a rather acute type, but usually of a more chronic character, sometimes very large (size of an infant's head) chronic abscesses or ulcers. The lesions are nearly always progressive with marked tendency to dissemination by lymph and blood stream, still sometimes they may heal eventually." The lungs show extensive miliary lesions, nodular consolidation sometimes with caseation, abscesses or massive consolidation. There are prone to be confluent aggregations of tubercles which may be exudative. Miller[29] reported a case of pulmonary involvement suggesting a primary infection of the tracheal and peri-broncheal lymph nodes, lymphatic spread along the bronchial tree with subsequent development of nodular lesions scattered through both lungs with a final miliary explosion through the lungs, liver, spleen and kidneys. The fact that the oldest lesion in many cases is in the tracheal and bronchial lymph nodes is believed significant of the inhalation mode of infection.

Histology: Microscopically, the disease is a granuloma with a cellular reaction to the infection. The reaction is intense and includes a marked proliferation of various types of cells, formation of new blood vessels with central ischemia and tendency to caseation and liquification. The initial lesion is a pin-point nodule consisting of an aggregation of various type cells. The general tendency of these is to enlarge, and

after reaching a maximum size, to form abscesses. Less frequently the nodules form flaccid, elastic tumour-like masses. Ophuls[4] believed that the stages in the development of the parasite determined the type of lesion. The histological picture shows a dense, cellular infiltration composed of epithelioid, lymph and plasma cells with a few giant cells of the Langhan's type. Definite tubercles are similar to those of tuberculosis with a central zone of epithelial cells, surrounded by a peripheral area of lymphocytes, plasma and giant cells with and without central caseation. A surrounding zone of necrosis may be absent.

Differential Diagnosis

The disease should be differentiated from tuberculosis, pneumonia, empyema, carcinoma, bronchiolitis, blastomycosis and glanders. In cases of pulmonary disease not definitely or typical tuberculous when the sputum is repeatedly negative for tubercle bacilli, especially if the patient has lived on the Pacific Coast, the sputum should be cultured for organisms other than Koch's bacillus. When the lymph glands are enlarged in such cases, one should be removed, stained and cultured.

Although there has been considerable confusion in the literature regarding blastomycosis, some authors considering the two diseases identical, and others as Benham[30] believing that blastomycosis should not be considered a clinical entity, much has been written about the differentiation of the two. The chief diagnostic points of practical importance are that

coccidioidal infection resembles tuberculosis with its greater predilection for the lymphatic system and nodules, and that it always reproduces in the animal tissues by endosporulation, never by budding as does Blastomyces. Glanders is immediately excluded by the character of its growth on culture media.

Diagnosis

The clinical and pathologic manifestations of coccidioidal granuloma so closely resembles those of tuberculosis, that it is only through the laboratory that a differential diagnosis may be made.

Specimens sent to the laboratory depend upon localized infection such as pulmonary involvement, meningitis, multiple subcutaneous abscesses with or without drainage, osteomyelitis and granuloma. Only a few positive blood cultures have been obtained. The following specimens are suitable for examination: pus - aspirated from an unopened abscess or obtained on a sterile swab; sputum - collected in the morning as for examination of tubercle bacilli preferably following saline mouth rinse; bone scrapings - collected on sterile swabs or in a small amount of sterile saline; spinal fluid - in sterile tube; biopsy or autopsy tissue specimens placed in 10% formalin; blood - 10 c.c. planted in 100 c.c. of 1% glucose broth. Direct examination: specimens may be examined in cover slip or hanging drop preparations direct or after clearing with 10% potassium hydroxide. The low power objective should be used with the light reduced. The addition of a small amount of

Gram's iodine serves to make the examination easier. The typical spherical, highly refracticle, double contoured capsules may be seen with endosporulation in the mature forms. For permanent mounts, slides may be stained by the methods of Gram and Ziehl-Nielsen. The organisms are Gram negative, and the capsule is acid fast, the protoplasm being colorless or blue. To overcome the shrinkage or distortion of the capsule, the Giemsa, hematoxylin, and Mallory's epsin and methylene blue stains may be used to produce good permanent mounts.

Cultural methods: All types of material may be cultured. The mold grows on mold ordinary culture media forming a tangled, intricate, meshwork of mycelia made up of septate hypha. In old cultures the hyphae break up forming chlamydospores.

Animal inoculation: Guinea pigs are ordinarily used for laboratory work, altho cattle, sheep, swine, dogs, rabbits and mice are susceptible to the organism. Fresh material or a saline suspension of culture may be employed. After male guinea pigs are inoculated intra-testicularly, an orchitis develops which is of early diagnostic value. The infection then becomes generalized leading to death in from four to six weeks. The gross findings at autopsy are similar to those tuberculosis, lesions being found in the spleen, lungs, omentum, liver, kidneys, and lymph glands. The pus is characteristic being thick and tenacious as compared to the caseous consistency found in tuberculosis. The typical capsules are present in pus and tissue sections. Before a definite diagnosis is made, the

spherical forms should always be demonstrated in the tissue of the patients or laboratory animals, for the vegetative form of the organism on solid media is not sufficiently characteristic except to the trained mycologist.

Immunologic tests: are still in the experimental stage, although it is probable that the endermal reaction will be of importance.

Therapy

A great variety of therapeutic agents has been tried in the management of coccidioidal granuloma, for the most part without success.

General treatment of patients with this disease should be the same as for those with tuberculosis. A high caloric, vitamin and mineral diet plus anti-anemic therapy is indicated. Amputation of an extremity or incision of a lesion serves to arrest unlocalized disease.

Iodine in various forms has been used alone or in combination by many investigators. Rixford[1] tried potassium arsenite, potassium iodide and mercurous iodide internally without benefit. Cooke[11] experimented unsuccessfully with iodine and arsphenamine. Childrey[31] combined antimony and potassium tartrate with potassium iodide. Chipman and Templeton[12] were unsuccessful using potassium iodide, iodine in aequeous solution, colloidal copper, typhoid vaccine and gentian violet. Davis[14] reported uncertain results from potassium iodide and deep X-ray therapy, with the best results

from amputation. Cummins and Saunders[13] were unsuccessful with emetin, crystal violet and ipecac. Lipsitz, Lawson and Fessenden[34] were unable to arrest a far advanced case by their treatment consisting of copper sulfate and potassium iodide.

Vaccines have been used with at best doubtful benefit, and shock with typhoid vaccine[12] has produced no results. The results of treatment with gentian violet and merchurochrome - 220 soluble do not warrant further trial.

Several apparent cures have been reported. Guy and Jacobs[33] reported beneficial results using roentgen rays and antimony potassium tartrate 1% intravenously. X-rays alone produced no apparent change, and there was much slower resolution during treatment when the roentgen rays were omitted. Tomlinson and Bancroft[34] used antimony and potassium tartrate intravenously on alternate days with good results. Three apparent cures are not conclusive, but no report has appeared with comparable results over several years.

Chapman and Templeton[12] obtained best results with iodides orally and intravenously. Glandular and cutaneous lesions improved in 75% of the cases, but osseus lesions were not changed. Smith[8] reported two cases apparently arrested by colloidal iodine intravenously.

Jacobson[19] used colloidal copper with fair results, and Sorsky and Nixon[35] with two apparent cures, concluded that colloidal copper, bismuth and gentian violet warrant further trial.

The most encouraging results have been obtained by Myers and Thienes[36] and Stockton,[37] who obtained apparent clinical improvement by means of thymol, oil of cinnamon, and oil of clove. Their results have been duplicated in an experimental study by Sox and Dickson,[38] using eleven drugs and a vaccine. The drugs included copper sulfate, novasural, bismuth potassium tartrate, iodobismitol, colloidal copper, sodium thiosulfate, potassium iodide, and thymol. Vaccine and a control were also used. Only thymol was found to give a definitely favorable effect, the experimentally infected animals treated with thymol living longer than the controls. In humans, an oral dosage of six grams daily is well tolerated and there are good results from local and systemic application.

At the present time, thymol seems to be the most promising therapeutic agent. With increased alertness in diagnosis, coccidoidal granuloma should prove to be less fatal in the future than it has been in the past.

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EXPERIMENTAL STUDY

Purpose: To determine the incidence and type of fungi in the sputum of patients with pulmonary tuberculosis.

Method: Routine cultures were made from the sputum of 31 cases of pulmonary disease classified as follows;

Pulmonary tuberculosis		28
incipient	5	
moderately advanced	18	
far advanced	5	
Pleurisy with effusion		2
Undiagnosed		1
	total	31

On the morning of the collection, each patient was given a hot, saline gargle, and instructed to expectorate a single specimen into a sterile Petri dish. The sputum was immediately planted on two tubes of Saboroud's media, one of which was incubated at 20 C. and the other at 37 C. Slants were kept for at least two weeks before being reported negative.

When a fungal growth was found, the above procedure was repeated on three successive days, before a positive report was made. Since the diagnosis of fungal infection depends partly upon the continued presence of a fungus in the sputum, cultures were made from the sputa of these patients bimonthly during the period of study.

Following the isolation of the fungus in pure culture, its carbohydrate reactions were observed as an aid in the deter-

mination of species. Since the sugar fermentations of the organisms were practically constant, only one set of reactions is recorded for each patient and are to be found in the table on the following page.

Result: Monilia albicans was isolated from the sputum of three cases.

1. M. W. - bilateral pulmonary tuberculosis with cavitation and bronchial asthma.

2. D. H. - bilateral pulmonary tuberculosis showing clearing.

3. E. W. - bilateral pulmonary tuberculosis with cavitation.

An undetermined species of Penicillium was found in one case of bilateral pulmonary tuberculosis and bronchiectasis for two months, but since it cannot be isolated at the present time, has been regarded as a contaminant.

Discussion: In the first case, the patient had severe bronchial asthma. Skin tests showed a strongly positive reaction to dust. Since dust frequently contains mold spores, the fungus in this case might be regarded as a contributing cause to the asthma rather than a factor complicating tuberculosis. The second patient is at present showing marked improvement. The third case is interesting because, despite the extensive cavitation of both lungs, Monilia albicans was repeatedly isolated before tubercle bacilli could be demonstrated in the sputum.

Despite the widespread opinion that Moniliae occur only as secondary invaders of tuberculous cavities, no fungus was

found in the sputa of the five cases of far advanced tuberculosis.

Conclusions: Monilia albicans was isolated from the sputum of three patients with tuberculosis. Statistically, the incidence may be represented as follows;

Total patients	31	
Patients with fungus	3	9.6%
Total cultures	104	
Cultures negative for fungus	72	
Cultures positive for fungus	32	30.7%

Carbohydrate Fermentations

Name	Day	Dextrin	Dextrose	Galactose	Inulin	Lactose	Levulose	Maltose	Mannite	Saccharose	Milk	Dextrose broth	Species
M.H.	2	-	AG	A	-	-	AG	AG	AG	-	-		
D.H.	2	-	AG	A	-	-	AG	AG	AG	-	-		
E.W.	2	-	AG	A	-	-	AG	AG	AG	A	-		
M.W.	5	-	AG	A	-	-	AG	AG	AG	-	++		
D.H.	4	-	AG	A	-	-	AG	AG	AG	-	++		
E.W.	4	-	AG	A	-	-	AG	AG	AG	Asl	++		
M.W.	7	A	AG	A	-	-	AG	AG	AG	?-	++	Sediment	M.albicans
D.H.	7	-	AG	AG	-	-	AG	AG	AG	?A	++	Sediment	M.albicans
E.W.	7	-	AG	AG	-	-	AG	AG	AG	A	++	Sediment	M.albicans

Presentation of Cases

Case No. 1

C.C. A 49 year old Irish male entered the hospital complaining of shortness of breath and easy fatiguability during the past 16 months.

P.H.: Measles, jaundice, malaria, peptic ulcer, T. & A, gonorrhea (1918) and a primary chancre treated locally (1919).

F.H.: Irrevelant.

Habits: Smoked 1 pack cigarettes per day. Liquor and beer occasionally.

Occupation: Business representative for machinist's union.

P.I.: Patient had always been well until the winter of 1934 when on walking in the cold he developed a pain in the upper half of the sternum which disappeared when he returned to his warm hotel. In December, 1937, he had an upper respiratory infection with the production of a small amount of sputum. Shortly after, he also noticed a fullness below the left costal margin associated with soreness of the left lateral chest walls. Palpitation of a few hour's duration was relieved by sitting up. Since then, there were frequent attacks of coughing producing small amounts of sputum. No hemoptysis or streaking. Gradual weight loss of 15 pounds since November, 1935.

P.E.: Lungs showed equal expansion on both sides. Tactile fremitus was decreased on both sides. Percussion revealed hyperresonance throughout. Breath sounds were roughened at

right apex posteriorally. In right interscapular space on deep expiration, there was tubular breathing with a suggestion of cavernous breath sounds. Sounds were suppressed at both apices. There were many sonorous and sibilant rales scattered throughout both lung fields.

Laboratory findings: urine negative. Slight secondary anemia. Blood sedimentation rate 5 mm / hour. Sputum negative for acid fast bacilli.

Diagnosis: Chronic bronchitis with emphysema. Bronchiectasis. Chronic myocarditis with general arteriosclerosis.

Treatment: Rest. Patient discharged to follow treatment at home.

Readmission: February 7, 1938. Since discharge the patient had become progressively and markedly worse. Loss of 18 pounds in weight. Two ounces of expectoration per day. Sputum examination revealed Monilia albicans on five occasions. Diagnosis: bilateral pulmonary moniliasis. Discharged unimproved. Patient died at home one week later.

Pathological report: The thorax was opened and an examination made of the lungs. Unfortunately this was not done until after the body had been embalmed, and the pleural cavity contained a large amount of strong formaldehyde. The lungs were therefore hardened and somewhat shrunken. In the upper lobe of the left lung in the outer posterior portion was an irregular consolidation. On section the tissue contained a number of small abscess cavities lying near the bronchi and exuding

a purulent material on pressure. The remainder of the lung appeared negative. The right lung in the upper middle lobe showed apparently some thickening but no purulent material was observed. The rest of the lung appeared normal.

Gross lung: Section of the right lung which measures 6.8 x 6.8 x 1.5 cm showed the pleural surface to be everywhere smooth and glistening, dark brownish-gray in color, and thrown up into numerous folds, presumably due to collapsed areas of emphysema. The cut surface of the lung was uniformly blackish-gray in color, and showed evidence of having been previously embalmed. The surfaces were definitely moist and exuded moderate amounts of fluid having a definite odor of formaldehyde. The alveolar markings were clearly visible and no areas of consolidation were seen. There were two sections of the left lung, the first measuring 9 x 7 x 1.4 cm. It was roughly oval in outline, presumably being taken from the upper or mesial aspect of the lung as its pleural surface was also thrown into numerous rugae and was everywhere smooth and glistening. The lung parenchyma was similar to that seen in the right lung, except that in addition, from the bronchioles, a thin, mucoid, yellowish-gray exudate could be expressed. There were also a few peribronchial areas from which similar material escaped, but there was no definite focus of consolidation.

The second section measured 6.8 x 3.8 x 1.5 cm. It was lined along one margin by intact, normal appearing pleura.

Its cut surfaces were similar to the other section from the lung.

Microscopic examination of the sections thru the infiltrated area of the left lung showed numerous small abscesses ranging from small accumulations of pus cells to areas 1-2 cm. in diameter. These abscesses appeared in the region of the bronchi. A purulent bronchitis was also present. In the walls of the abscesses, adjoining the interstitial tissue of the lung, mycelial filaments and irregularly staining cells were observed. These organisms were only found in sections from the abscessed area. Sections from the right lung and from other portions of the left lung showed only a bronchitis and no abscess formation.

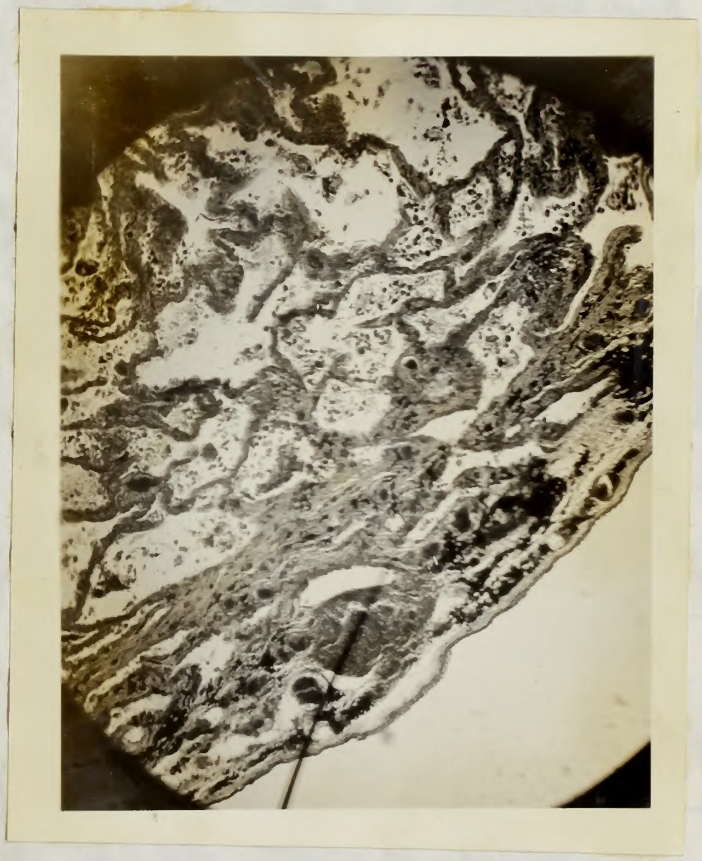
Smears of the pus showed only staphylococci. Cultures were made of the purulent material and from the abscessed areas in the left lung. No growth was obtained because of the disinfecting action of formaldehyde. The finding of a mycelium and cells in the walls of the abscess, in view of the cultural results in obtaining Monilia albicans from the sputum, gives fairly conclusive, but not absolute, proof of a primary moniliasis. Unfortunately, these findings could not be corroborated by the final criterion of growing organisms from the lung tissue.

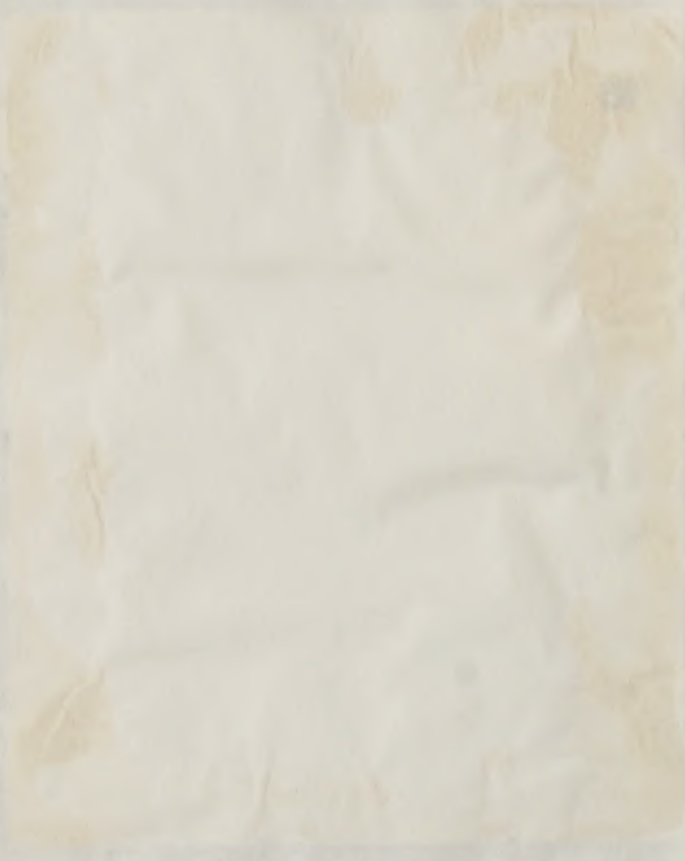
Anatomical diagnosis: Multiple pulmonary abscesses of the left lung with the presence of Monilia and staphylococcus. The condition should be interpreted as pulmonary moniliasis.

Case # I

Photomicrographs of Lung Sections

Magnification : 100 X





Milk	Saccharose	Mannose	Maltose	Levulose	Lactose	Inulin	Galactose	Dextrose	Dextrin	Day	Strain
-	?	AG	AG	AG	-	-	A	AG	AG	2	A
-	?	AG	AG	AG	-	-	?	AG	AG	2	B
semi	A	AG	AG	AG	-	-	A	AG	AG	4	A
-	A	AG	AG	AG	-	-	A	AG	AG	4	B
semi[x]	A	AG	AG	AG	-	-	A	AG	AG	7	A
semi[y]	A	AG	AG	AG	-	-	A	AG	AG	7	B
-	A	AG	AG	AG	-	-	A	AG	A	2	A
-	A	AG	AG*	AG	-	-	A	AG	A	2	B
-	A	AG	AG	AG	-	-	A	AG	A	2	C
-	A	AG	AG*	AG	-	-	A	AG	A	2	D
-	A	AG	AG*	AG	-	-	A	AG	A	2	E
≠	A	AG	AG	AG	-	-	A	AG	A sl red	4	A
≠	A	AG	AG	AG	-	-	A	AG	AG red	4	B
≠	A	AG	AG	AG	-	-	A	AG	AG sl	4	C
≠	A	AG	AG	AG	-	-	A	AG	A red	4	D
≠	A	AG	AG	AG	-	-	A	AG	AG sl	4	E
≠	A	AG	AG	AG	-	-	A	AG	A	7	A
≠	A	AG	AG	AG	-	-	A	AG	AG*	7	B
≠	A	AG	AG	AG	-	-	AG	AG	AG*	7	C
≠	A	AG	AG*	AG	-	-	A	AG	A sl	7	D
≠	A	AG	AG*	AG	-	-	A	AG	AG*	7	E

* means gas given off but tube not filled.
In tubes marked sl or red, the color had not faded to yellow as is usual.
x - coagulation in 12 days. y - no coagulation in 12 days.

Case No. 2

M.G. - female , aged 54 , was transferred to the Norfolk County Hospital with a diagnosis of chronic bronchitis and asthma.

P.H. : Patient had been well until the age of ninae when she had measles and mumps. She went to work at the age of 21 , doing office and shop work , and since then, housework.

Had pneumonia in 1920,1925, 1932 and 1934. Has had frequent attacks of pleurisy since 1915. Was treated at the Quincy City Hospital from 2-4 to 2-22-38 for asthma and bronchitis.

F.H. : Father died of "shock". Mother died of lobar pneumonia. Two sisters and two brothers died of tuberculosis.

P.I. : History of exposure to tuberculosis from two brothers and two sisters. Patient has not been strong since pneumonia in 1932 and 1934. Coughs and raises copious amounts of sputum.

P.E. : of lungs reveals numerous rales scattered over both lung fields.

X-ray : of chest shows fibrosis with no evidence of infiltration or cavitation.

Lab. Data : 72 sputum specimens, 21 of which were concentrated, from March 11,1938 to April 5, 1939 have been negative for tubercle bacilli. Four cultures showed no growth of tubercle bacilli. 1 guinea pig inoculated April 5,1939 shows no gross or microscopic evidence of tuberculosis. Eight stool specimens were negative for tubercle bacilli. Monilia was isolated from the sputum on three occasions.

Hinton negative.

Tuberculin test : 1 : 10,000 negative

, 1 : 1,000 negative

1:: 100 positive

Treatment : Patient was treated with potassium iodide and bed rest. She has improved steadily and is now tolerating guarded exercise. X-rays of the chest show continual clearing of the lesions. At the present time , examination of the sputum reveals no Moniliae present.

Dr. Derow's note : " It is probable that this patient has bronchiectasis , the remissions and exacerbations of which can explain her frequent illnesses variously diagnosed as pneumonia, bronchitis, asthma , and tuberculosis. As to whether Moniliae are the primary invaders , or secondary concommitants in this bronchiectatic process is very difficult to state. At any rate, it would seem that at present they have become the determining factor in her physical condition. "

Carbohydrate Fermentations

History number		Day	Dextrin	Dextrose	Galactose	Inulin	Lactose	Levulose	Maltose	Mannose	Saccharose	Milk	Dextrose broth
#2	A	2	-	A	-	-	-	A	-	A	A	-	
	B	2	-	A	-	-	-	A sl	-	A	-	-	
	A	5	-	AG	A sl	A sl	-	AG	-	AG	AG	+	
	B	5	-	AG	-	-	-	AG	-	AG	-	Semi	
	A	7	-	AG*	A	A	-	AG	-	AG*	AG*	++x	Sediment
	B	7	-	AG	-	-	-	AG	-	AG	-	++x	Top growth
#3		2	-	AG	-	-	-	A	-	AG	-	-	
		4	-	AG	-	-	-	AG	-	AG	-	-	
		7	-	AG	-	-	-	AG	-	AG	-	-	

* Indicates that the acid reaction was over to a good yellow. In other cases the red did not entirely fade and the small tube was more acid than the surrounding medium.

x Indicates that upon rechecking the milk and incubating for 3, 10, 15 and 19 days there was no coagulation.

Case No. 3

J.W.R.: Male, aged 30, entered the out-patient department of the Charlestown State Prison Oct. 17, 1938, with his chief complaints persistent cough and generalized weakness.

P.I.: Onset was that of a chest cold, characterized by deep seated, non-productive cough since Aug. 26, 1938. Patient's condition during the next month became progressively more severe with marked weight loss. Because of continual coughing and repeated vomiting, patient was admitted to hospital Oct. 21st for further treatment. X-ray examination of chest done at that time was negative. Repeated sputum exams were always negative for acid fast bacilli. Since admission to the hospital, patient's course was steadily downhill with persistent coughing, vomiting, loss of weight, weakness, occasional night sweats and temperature intermittent between 99 and 102° F. He was transferred to Norfolk State Prison Colony Dec. 22, 1938.

P.H.: Patient had always been in good health with no serious illnesses, injuries or operations. Denied gonorrhea and syphilis.

F.H.: Father, mother, brother and sister alive and well. No family history of tuberculosis, diabetes, epilepsy, cancer, or allergy.

P.E.: Revealed fairly well developed chronically ill, male lungs. Expansion of left chest was greater than that of the right. Lungs were dull to percussion posteriorally from

scapular angle downward. Breath sounds throughout both lung fields were distant and vesicular. Medium moist râles could be heard at both bases. Heart examination was normal, Rate 110. B.P. 80/60. Few left sided cervical glands were palpable but not markedly enlarged or tender. Rest of P.E. essentially negative.

Admission Diagnosis: 1. Miliary tuberculosis
2. Fungal infection of lungs

X-rays: Chest films showed diffuse mottling throughout both chests consistent with miliary tuberculosis, although the lesions were larger than ordinarily seen. There was a small amount of fluid at the extreme right base, and an area in the lower lobe consistent with cavity formation.

X-ray diagnosis:
1. Miliary tuberulosis
2. Multiple emboli
3. Fungal infection

X-ray of the pelvis and long bones taken to rule out metastases to the lung from the bones were negative.

Lab. Data:
Hinton negative
Urine negative. Culture for acid fast bacilli negative.
Blood: Hbg 60-74% Sahli
RBC 3.7-5.00
WBC 24,000-35,000
Smears showed slight to moderate achromia.
Lymphocyte monocyte ratio = 72:28

Sedimentation rate: 95 mm in one hour.

Sputum: 23 concentrated specimens were negative for tubercle bacilli. Four cultures and two guinea pig inoculations were negative. Three specimens of gastric content re-

vealed no acid fast rods. An atypical species of Cryptococcus was isolated from the sputum on 8 occasions.

Progress: Temperature was intermittent between 98 and 102°F. Cough persistent and productive of 4 ounces thin, gray sputum daily. One course of sulfanilimide was given and discontinued due to lack of response. Because of repeated, unsuccessful search for tubercle bacilli, high white count, consistent presence of yeasts in sputum, and negative reaction to PPD of tubercle bacilli, potassium iodide was started. Patient developed a secondary anemia which was treated with transfusions.

During his stay in the hospital, his course was steadily downhill with continued loss of weight and strength, and increasing spread of the process in both lungs. Patient expired Feb. 24, 1939. Final diagnosis of chronic pulmonary infection probably due to yeasts.

Although the strongest arguments for autopsy were presented to the patient's family, permission could not be obtained.

Summary

A review of the literature of Aspergillus, Monilia, and Coccidioides as etiologic agents in the production of pulmonary mycoses is presented.

The results of a study for fungi of the sputa of 31 tuberculous patients are reported. The only fungus isolated from such sputa was Monilia albicans with an incidence of 9.6% (3 cases out of 31 patients).

Three unpublished cases of probable primary pulmonary mycoses are reported.

There are three explanations for the presence of fungi in the sputum collected with due precautions against contamination:

1. The fungus may be a saphrophyte.
2. It may represent a secondary invader.
3. The fungus may be pathogenic and the primary agent in the production of the disease process.

In early diagnosed cases where the fungus is proven the sole etiologic agent , efficacious treatment is often possible. The essential features in the diagnosis of such conditions are :

1. The constant presence of a pathogenic species of fungus in the sputum.
2. The isolation of it in pure culture and its subsequent identification by means of any desired procedure.
3. The gradual clinical improvement of the patient with the concurrent disappearance of the fungus from the sputum.

It is often desirable, but not essential, to use animal inoculation to prove the pathogenicity of the fungus for the laboratory animal even though such a proceedure does not always show the relationship of the organism to the disease in man.

Although serologic and endermal reactions are not considered entirely satisfactory and absolutely specific at the present time, the results of such tests are desirable in the interests of accumulating more exact knowledge.

The results of this study seem to indicate :

1. Pulmonary mycoses are definite clinical entities.
2. Fungal infections of the lung probably occur with much greater frequency than is ordinarily supposed.
3. Some chronic pulmonary infections produced by molds are mistakenly diagnosed and treated as tuberculosis.
4. All cases of obscure pulmonary infection not definitely or typically tuberculous in nature should have the sputum cultured for fungi.

Although there is an abundance of literature on the subject of pulmonary mycoses , there remain definite limitations to our knowledge. We are ignorant of the incidence of fungi as primary and secondary invaders of the lung. We do not know the association of molds with acute respiratory disorders, or how such organisms predispose one to tuberculosis. We are still unaware of how fungal infection impedes or inhibits the recovery of patients with pulmonary tuberculosis.

In view of these facts , it seems desirable that further investigation be conducted on the subjects of primary pulmonary mycoses , and tuberculosis concurrent with fungal infection.

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